United States Court of Appeals

for the Second Circuit

EXHIBITS

74-1738 ORIGINAL

In The

United States Court of Appeals

For The Second Circuit

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION, and SOLGAR, CO., INC.,

Plaintiffs-Appellants,

vs.

CASPER W. WEINBERGER, Secretary of Health Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants-Appellees.

On Appeal from the United States District Court for the Southern District of New York.

EXHIBIT VOLUME

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In bovine articular cartilage which possesses an exceedingly low respiration and thereby a relatively higher aerobic glycolysis than the other tissues mentioned, the inhibition averaged 57 per cent.

Results of a representative experiment with calf cartilage are listed in Table 1. It is seen that glucose

TABLE 1

THE ACTION OF GLUCOSE ON THE RESPIRATION OF CARTILAGE*
Mean rates over three hour period

Substrate	None	Glucose	Pyruvate	Succinate	Glucose + Pyruvate	Glucose + Succinate
	(M 1m)	(M 20)	(M 25)			
Q_{O_2}†	.079	.029	.079	.103	.062	.080
Inhibition by Glucose	...	.050 (63%)	...	...	.017 (22%)	.023 (23%)
Acceleration by Pyruvate and Succinate	...	...	0	.024	.033	.051

† Cmm. O_2 / mg dry weight hour.
* Articular cartilage from the metacarpal phalangeal and metatarsal phalangeal joints of a calf two months old. About 125 mg dry weight of cartilage slices per experimental vessel. h_H = 7.38
Gas: Air Medium: Phosphate-Ringer's

retards oxygen consumption by 63 per cent. Similar effects were obtained by the addition of mannose, but no effect was obtained with fructose which is not glycolyzed by cartilage. The inhibition observed in oxygen (53 per cent.) was of the same order as in parallel determinations in air (59 per cent.). The magnitude of the respiratory inhibition in cartilage is neither due to a drop in the pH of the medium incident to the high rate of acid formation after the addition of glycolyzable hexoses to the slices nor to an accumulation of glycolytic splitting products or their derivatives (lactate, pyruvate, succinate). Table 1 shows an example of the results obtained with pyruvate and succinate. Pyruvate does not alter the rate of the spontaneous O_2 consumption, but it induces an acceleration of the oxygen uptake if the respiration is inhibited by glucose. Succinate* accelerates respiration in the presence of glucose to a greater extent than in its absence. Apparently the addition of glucose suppresses cellular processes which result in the formation of pyruvic and succinic acids since the addition of these acids abolishes more than half of the respiratory inhibition by glucose (*cf.* Table 1).

Elliott and Baker[8] as well as Victor and Potter[4] observed that the retardation of respiration by the addition of glucose was paralleled by a rise of the R.Q., indicating a replacement of respiratory substrates of the tissue by the added glucose. The latter authors pointed out that the change of the R.Q. after the addition of glucose was compatible with a shift from protein oxidation to carbohydrate combustion. Warburg and colleagues[9] showed that the formation of ammonia in tissue slices deprived of glucose is especially high in glycolytically active tissues and that the addition of glucose inhibited the excretion of ammonia. This inhibition was considered an expression of the protein sparing action of glucose. The investigation of Dickens and Greville[10] indicate that the oxidation of glucose rather than its glycolysis is responsible for the retardation of the protein catabolism. It seems possible that the addition of glucose causes a decrease of oxygen consumption in such tissues in which the hexose is not oxidized with the same velocity as the cellular substrates, the oxidation of which it replaces. Such a mechanism would explain the frequent occurrence of the Crabtree effect in aerobically glycolyzing tissues where a relatively sluggish oxidation of glucose coincides with a high protein catabolism in the absence of sugar.

This tentative explanation does not intend to imply that glucose oxidation replaced only the combustion of protein nor that glycolysis does not prevent to a certain extent protein catabolism, as was suggested by Warburg.[9] The explanation supports the view, however, that the Crabtree effect is not a reversal of the checking action of respiration on glycolysis but a separate process which indicates the sparing of cellular substrates by the combustion of extracellular glucose. Thus, the Crabtree effect may belong to the reactions which underlie the stimulative action of respiration on cellular anabolism (Pasteur effect b).

The mechanism of the effect is being investigated further.

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* Lactate behaves similarly.

APPEARANCE OF SKELETAL ABNORMALITIES IN THE OFFSPRING OF RATS REARED ON A DEFICIENT DIET

THE following observations were made when rats, which were reared on deficient diets, were bred. All rats used were of the Sprague-Dawley strain. One group of females was reared on a diet consisting of yellow cornmeal 76 per cent., wheat gluten 20 per cent., calcium carbonate 3 per cent., sodium chloride C.P. 1 per cent. (Steenbock and Black rachitogenic diet No. 2965),[11] which was supplemented with viosterol (each rat received 60 I.U. every tenth day). On this diet the animals were retarded in growth and

[8] O. Warburg, K. Posener and E. Negelein, *Biochem. Zeit.*, 152: 309, 1924.
[9] F. Dickens and A. Greville, *Biochem. Jour.*, 27: 1123, 1933.
[11] H. Steenbock and A. Black, *Jour. Biol. Chem.*, 64: 263, 1925.

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development. The vagina opened at the age of three to four months, the regular cycles started at between four and five months, the first matings took place at between five and six months, at which age the rats weighed only about 150 grams. In this group of 18 animals, 32 pregnancies were observed. A total of 164 young was born either spontaneously or by cesarean section; of these, 107 were apparently normal, while 57 presented multiple congenital abnormalities.

An abnormally short mandible was found in 39 animals. This defect was so marked that the tongue was exposed to a large extent. Many animals also had deformed extremities. Syndactylism of different grades was observed in 32 young. A short tail was seen in 12 animals. One hundred and four of the young were cleared by the Spalteholz method to facilitate the study of the skeleton. In 42 of these specimens the lower legs showed reduction in size or absence of the tibia; in 20 the fibula was shortened or absent; in 22 there was fusion of the ribs; and in 14 there was fusion of the centers of ossification of the sternum.

Another group of females of the same strain was reared on a more adequate diet consisting of yellow cornmeal 78 per cent., wheat gluten 18 per cent., calcium carbonate 1 per cent., sodium chloride C.P. 1 per cent., and dried pig liver 2 per cent.[2] This diet resulted in much better growth and development of the animals. This group consisted of 24 females which had 39 pregnancies resulting in 294 young. None of the latter showed deformities of the mandible or extremities like those described in the previous group. The only external abnormality observed in the offspring of the animals on this diet was absence of the tail in one animal. Eighty of the 294 young were cleared, but they showed none of the skeletal deformities found in the previous group.

A third group of 12 female rats of the Sprague-Dawley strain was raised on an adequate diet (Bill's modification of Steenbock's stock diet).[3] Thirty litters born to these animals consisted of 216 young. One abnormal animal was noted in this group. It weighed only 2½ grams and when cleared showed short femurs and an abnormal sternum. One hundred and nineteen young in this group were cleared, but they showed no abnormalities.

At the present time we are extending these experiments along both genetic and nutritional lines.

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[1] W. F. Remington, *Jour. Nutrition*, 13: 233, 1937.
[2] C. D. Bills, E. M. Honeywell and W. A. MacNair, *Jour. Biol. Chem.*, 76: 251, 1928.

MODIFICATION OF THE CHEMISTRY AND PHARMACOLOGICAL ACTION OF THE CARDIAC GLYCOSIDES[1]

Alteration of the molecular structure of a drug frequently results in modification of its pharmacologic action. The digitalis bodies exist in nature as chemical combinations of one or more sugars with hydroxylactones of sterol hydrocarbons. This suggests the possibility of modifying the digitalis bodies by replacing the sugar with a vasodilator, thus obtaining a cardiac glycoside molecule which might embody the desirable therapeutic actions of both drugs.

Two molecules of theophylline can be combined chemically with one molecule of a genin obtained by removing the sugar radical from a squills glycoside.[2] This dimethylxanthine genate can be prepared as short needle like yellow crystals having a molecular weight of 758.2 and an empirical formula of C38 H46 O9 N8 (presumably C24 H28 O3 (C7 H7 O2 N4) 2 2H2O). When injected intravenously in cats the lethal dose of this theophyllinated genin is much greater than that which might be expected on the basis of the amount of genin used in its preparation. The lethal dose of a mechanical mixture of theophyllin and the genin, on the other hand, is in proportion to its genin content. The theophyllinated genin, the squills glycoside, the mechanical mixture, and also digitalis show the same progression of electrocardiographic changes; T wave inversion and ventricular premature beats occur with the same degree of frequency, while nodal rhythm and ventricular tachycardia appear after approximately the same percentage of the lethal dose. Changes in the S-T segment, however, appeared in a far lower percentage of the animals given the theophyllinated genin than in those given digitalis, squills glycoside or a mechanical mixture of theophyllin and the squills genin.

These preliminary studies suggest that dimethylxanthine and the squills genin have been combined in a single molecule retaining some of the digitalis-like properties and modifying others. Further studies of the chemical and pharmacological properties of this preparation are necessary as well as clinical studies to ascertain the therapeutic value of the drug.

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THE NATURE OF THE ANTI-ALOPECIA FACTOR

It has recently been shown[1] that the mouse requires a new vitamin for normal growth and for mainten-

[1] From the Medical Research Department of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.
[2] This preparation was supplied by Parker Dorn, Inc., Worcester, Mass.
[3] D. W. Woolley, *Jour. Biol. Chem.*, 136: 113, 1940.

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Hypervitaminosis A

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(*Received* 22 *March* 1945)

Many forms of injury are known to occur in experimental animals when they are dosed with greatly excessive amounts of oils or concentrates containing vitamin A. Takahashi, Nakamiya, Kawakami & Kimura (1925) tested the effect of excess of their crude concentrate 'Biosterin' when given orally to rats and mice, and observed loss of hair, emaciation and paralysis of the hind legs. After periods varying from a few days to several weeks the animals died, and at autopsy fatty degeneration of the liver,

kidney and heart was found, together with hyperæmia, and sometimes haemorrhage in the intestines and lungs. Both Takahashi *et al.* and later Matsuoka (1934) found that excess of vitamin A concentrate was also toxic when injected, usually causing death with cramp in less than an hour. The principal observations of the Japanese workers in regard to the ill effects of excess of vitamin A concentrates when given orally were confirmed by Harris & Moore (1928), Chevallier, Cornil & Chabré (1934), Simola & Kalaga (1934), Lewis & Reti (1934), Ypsilanti (1935) and Ocana (1935).

Another remarkable lesion, which escaped notice until highly potent concentrates became available, was described by Collazo & Rodriguez (1932) and Bonskov & Seeman (1933). The skeletons of rats which had received excess of concentrate became so fragile that the animals incurred fractures of the large bones of the legs and shoulders in the course of the limited movements possible while in captivity in small cages. Sometimes the broken ends of the bone were ankylosed with the formation of large irregular calluses (Davies & Moore, 1934). Further observations on these skeletal lesions were made by Strauss (1934), Hoff & Jodlbauer (1934), Vedder & Rosenberg (1938) and Wesaw, Wronski, Wroblewski & Wroblewski (1938). Recently, a further injury has been reported by Rudolph & Moore (1943), whose rats often died from severe internal haemorrhage after receiving excess of rich sources of vitamin A. This bleeding was much more profuse and sudden than the diffuse bleeding in various membranes described by previous workers. If not a distinct phenomenon it must at least be considered a separate aspect of a general liability to haemorrhage.

While, however, it is well established that concentrated sources of vitamin A are toxic when given in great excess, some doubt has remained as to whether vitamin A itself is responsible for the toxicity, and if so whether it produces all, or only some of the lesions which have been reported. Undoubtedly fish liver and body oils may be injurious for several distinct reasons unrelated to their content of vitamin A. Agduhr (1926, 1928) noticed the ill effects of cod-liver oil on the musculature of various animals, and pointed out that the oil was still injurious after its vitamin A had been destroyed. Shimoto (1934) and later Yoshida (1937) concluded that the glyceride fraction, and not vitamin A, was responsible for the adverse action of any marine oils on rats. Hartwell (1927), who noted that female rats succumbed to uterine haemorrhage when allowed to become pregnant on a diet containing cod-liver oil, tentatively ascribed this effect not to vitamin A but to the destructive action of the oil on the vitamin E in the diet. In our [illegible] oil is toxic to rats on account of [illegible] alcohol, which results also in destruction; while we have found a stale specimen of sardine oil to be toxic although devoid of vitamin A. It must also be remembered that concentrates rich in vitamin A are often equally rich in vitamin D, which is known to be toxic when given in great excess. Even the original experiments of Takahashi *et al.* (1925) may now be taken as evidence that the toxic effects observed were not all due to vitamin A, since a preparation made from seaweed, and presumably free from preformed vitamin, was no less toxic than their cod-liver oil concentrates.

In crude sources of vitamin A, therefore, many components other than the vitamin might well be responsible for toxicity. Experience with comparatively pure concentrates, moreover, has also suggested to some investigators that the vitamin may not be implicated after all. Although Drigalski (1933) found that concentrates given orally to rats were harmless if the vitamin had been destroyed by ultra-violet irradiation, Matsuoka (1934) observed convulsions in rats after the injection of concentrates which had been freed from vitamin by oxidation or hydrogenation. Conversely a distillate containing the vitamin was not toxic. Hansen (1935), who prepared various crystalline derivatives of vitamin A, found that toxic factors accompanied vitamin A into the unsaponifiable fraction, but could be separated by their inferior solubility in methanol. The purified vitamin did not appear to be toxic. Finally, Vedder & Rosenberg (1938) found no close relationship between vitamin A content and toxicity, as measured by the incidence of bone fractures, in distillates prepared from jewfish liver oil.

The main purpose of the present experiments, of which a preliminary description has already been given (Moore & Wang, 1943), has been to test the toxicity of vitamin A in its purest available form, i.e. as a crystalline ester. The uterine haemorrhage described by Hartwell (1927) has also been investigated to decide whether vitamin A may not be directly involved. The opportunity has also been taken to test the claims of Vedder & Rosenberg (1938) and others that liberal doses of vitamins C and D are beneficial to animals given excess of vitamin A concentrate.

EXPERIMENTAL

The toxicity of pure vitamin A acetate to young rats

Exp. 1. A specimen of crystalline vitamin A acetate ($E^{1\%}_{1\,cm.}$ = 1560 for the acetate) was kindly provided by British Drug Houses Ltd. To facilitate administration to rats it was dissolved in arachis oil. Five young male rats weighing 60–70 g. were given a basal diet consisting of casein 200, sugar 500, dried yeast 150, and salt mixture 50 parts. A measured amount of the solution of vitamin A acetate, equivalent to 50,000 i.u. daily during the first days of

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[illegible] was given to the animals, after [illegible] received with 5 g. of [illegible] which [illegible] given daily for the rest of the [illegible] first 4 days the dose of vitamin was [illegible] i.u., and some of the animals [illegible] kept the previous dose.

On the eighth day of the experiment a lowering [illegible] tenderness in the legs, was observed in some of the animals. X-ray examination [illegible] the ninth day revealed fractures of the tibiæ in [illegible] animals, and the general condition of all the animals was poor. By the twelfth day all the rats had sustained fractures. They had to be killed to avoid additional fractures during X-ray examination. Exophthalmos was seen in all cases, and in one rat a discoloration around the eyes was observed. Post-mortem examination revealed subcutaneous and intramuscular haemorrhages in some of the animals.

X-ray photographs were taken of the rats after excess of vitamin A had been given for 20 days (Pl. 3). It will be seen that the bones become abnormally thin. In one case only there was detachment of the epiphysis from the shaft of the bone, a lesion frequently observed in rather different form in human infantile scurvy. Fractures occurred most often, however, near the centre of large bones. The ends of the bones were sometimes ankylosed with the formation of calluses.

Exp. 2. Young male rats of weight 48–86 g. were given a basal diet similar to that used in Exp. 1, but the dried yeast was increased to 100 parts with a view to improving appetite. Group 1 ('Control') of five animals received 4·5 g. of the basal diet daily mixed with 1·5 g. of plain arachis oil. The vitamin A allowance was 1080 i.u. per week. Group 2 ('Vitamin A excess') received the same diet, but the arachis oil contained 40,000 i.u. of vitamin A acetate daily. Group 3 ('Oxidized vitamin A') had the same diet as group 2, but the oil had been aerated on a boiling water-bath until the vitamin A, as measured by the antimony trichloride reaction, had all been destroyed.

In the group given excess of vitamin A acetate one rat had a limb fractured after 7 days, while within 14 days all the rats in this group had fractures. The animals were miserable in appearance, and gained no weight during the experiment. At autopsy intramuscular haemorrhages were found in some instances. In contrast the rats, both in the control group and in the group given oxidized vitamin A, remained well, had neither fractures nor haemorrhage, and made average gains in weight of 18 and 12 g. respectively during the first 14 days of the experiment.

Mineral content of the bones in hypervitaminosis A. The ash content of the fat-free tibiæ of the control group on a fat-free basis was 52·1%, while for the group given excess of vitamin A the ash content was 51·3%. Contrary to expectation no significant difference was therefore detected in hypervitaminosis A.

Ascorbic acid and hypervitaminosis A. In parallel with the preceding groups another five rats were given excess of vitamin A, but with the addition of 10 mg. daily of ascorbic acid. Two animals had fractures on the seventh day of the experiment, and the remaining three had developed fractures, and were in a miserable condition, when they were killed between the ninth and eleventh days. At autopsy intramuscular or subcutaneous haemorrhage was found in all these rats. The ascorbic acid did not therefore alleviate the injurious effects of the excess of vitamin A at the doses in which the two vitamins were given.

Estimations of ascorbic acid by the indophenol method in the livers, adrenals and urine of the preceding groups 1 and 2 also failed to reveal any significant effect of excessive vitamin A on ascorbic acid metabolism:

	Mean wt. of liver (g.)	Ascorbic acid in Liver (mg./g.)	Adrenals (mg./g.)	Urine/rat for 24 hr. (mg.)
Group 1 (control)	6·0	0·11	3·7	0·4
Group 2 (excess of vitamin A)	5·3	0·09	3·3	0·4

Calciferol and hypervitaminosis A. Five more rats received the same diet with excess of vitamin A, and with the addition of 1 mg. daily of calciferol. Fractures developed in all these animals within 11 days, and in some rats haemorrhagic lesions round the eyes were noticed. At autopsy no intramuscular haemorrhage was found, but the muscles of the legs had a purple colour suggestive of venous congestion.

The injection of vitamin A. When young rats were injected with massive doses of vitamin A their reaction never amounted to more than a temporary cramping and twitching of the muscles of the hind legs. In no instance did an animal die as the result of this treatment.

In six rats, which had single doses of 40,000–90,000 i.u. of vitamin A acetate dissolved in arachis oil by either intraperitoneal or subcutaneous injection, no cramping, nor any other injury, was observed. Another animal received an intraperitoneal injection of about 40,000 i.u. of free vitamin A alcohol, prepared from the acetate and dissolved in arachis oil, without developing cramp. An intraperitoneal injection of 25,000 i.u. of vitamin A as halibut-liver oil, however, caused cramping in one rat after 40 min. The condition persisted for over 2 hr., but the rat had recovered by the following

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Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1. Normal rat.

Fig. 2. Hypervitaminosis A of 20 days' standing. Among the abnormalities are: (i) fractured femurs; (ii) fractured tibia; (iii) ulna and radius are abnormally thin.

Fig. 3. Hypervitaminosis A. Another rat. Fracture of radius and detachment of epiphysis from shaft of bone.

Fig. 4. Hypervitaminosis A. Another rat. Fracture of tibia and fibia. The bones are ankylosed with callus formation.

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[illegible] of rats of 70–90 g. [illegible] were injected [illegible] with 0·5 c.c. [illegible] of a 1 in 10 emulsion [illegible] with [illegible] saline. [illegible] were [illegible] with [illegible] and [illegible] test. [illegible] rats [illegible] received [illegible] of a [illegible] oil concentrate of cod-liver oil containing [illegible] of vitamin A [illegible] showed [illegible] cramping [illegible] for an hour, but recovered. The third [illegible] remained [illegible] for a short time, but had no [illegible] and recovered rapidly. Both [illegible] in which [illegible] was observed it was difficult to decide whether the cramp was [illegible], or merely the voluntary effort of the animal to adopt a position to overcome the [illegible].

The effect of excessive vitamin A on gestation in the rat

Several series of experiments were carried out to decide whether the uterine haemorrhage observed by Hartwell in pregnant rats given large amounts of cod-liver oil can be ascribed to vitamin A. The usual procedure was to take mature females, which had received a mixed diet of natural food-stuffs, and to place them together with males until spermatozoa were detected in the vaginal smear. The male was then removed, and the diet of the female was changed, immediately or after an interval, to a purified ration which contained vitamin A dissolved in an oily medium. In most of the experiments the diet used contained casein 20%, sugar 40%, dried yeast 5%, salt mixture 5%, and fat 30%, the solid components and fat being mixed together just before feeding. In some experiments the composition of the diet was varied slightly, the main differences being a reduction in the fat to 20% and the replacement of the dried yeast by an equal amount of marmite. No evidence was obtained to suggest that these minor alterations significantly affected the course of gestation. On the other hand, the incidence of haemorrhage was vitally affected by the stage at which excess of vitamin A was introduced into the diet.

Massive doses of vitamin A. Vitamin A acetate was given at the rate of 45,000 i.u. daily made up in arachis oil as 20% of the diet. Other rats received 30,000, 50,000 i.u. vitamin A daily as halibut-liver oil. The specimen used was kindly supplied by Allen & Hanburys Ltd., and contained 50,000 i.u. g. It was diluted with arachis oil to make 30% of the diet. Similar results were obtained with both sources of vitamin A and for the sake of simplicity they may be combined (see table at head of next column). Haemorrhage was first noticed between the fifteenth and twenty-first day of pregnancy in different animals. Inspection at autopsy of the uteri of rats which had died from haemorrhage suggested that the bleeding occurred at the junction of the placenta

Vitamin A given	Total no. of rats in group	No. of cases of: Uterine haemorrhage	Failure of implantation or resorption	Litters, dead or alive, without fatal haemorrhage
(*a*) Within 10 days after coitus	13	6	6	1
(*b*) More than 10 days after coitus	12	0	0	12

and endometrium. The placenta was sometimes partially detached, and the endometrium eroded. Histological examination indicated the presence of extensive extravasations of blood at the junction of the placenta and endometrium, but in view of the presence of maternal blood sinuses in this region during normal pregnancy the certain detection of abnormality was difficult. In agreement with the view that the retro-placental haemorrhage had occurred suddenly the structure of the foetuses appeared to be more or less normal.

It must be emphasized that litters have been counted as 'delivered' whether alive or dead. In practice the animals could not be watched continuously, and often it was difficult to decide whether neglected litters had been born alive or dead. Even when the young were born alive they were not reared unless the mother's ration was changed to a mixed diet of natural food-stuffs.

High doses of vitamin A. A veterinary cod-liver oil 'compound', containing 500 i.u. of vitamin A g., was given as 20% of the diet from the time of fertilization. The daily intake of vitamin was about 1000 i.u. The results were:

	Total no. of rats	No. of cases of: Uterine haemorrhage	Failure of implantation or resorption	Litters, dead or alive, without fatal haemorrhage
Vitamin A given at coitus	6	1	1	4

In this experiment marmite was given in place of the usual dried yeast. In one of the four rats which survived parturition the latter was accompanied by more profuse haemorrhage than is usual. Of five other rats which were given the oil as 30% of their diet, four had litters. In the remaining rat no signs of implantation were found at autopsy.

Dosing with marine oils low in vitamin A. A stale specimen of sardine oil, several years old and brown in colour, was given to two rats as 30% of the diet from the time of coitus. Fresh whale oil was given to six other rats. For the purpose of another in-

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...ed ... of the oil was ... but for 4 months ... animals had been ... the whole ... test. The results were:

	No. of rats	Uterine haemorrhage	Failure of implantation or resorption	Litters, dead or alive, without fatal haemorrhage
...	2	0	1	1
...	3	0	1	2
...	3	0	3	0

Both rats having sardine oil declined in weight throughout the experiment and became very emaciated. Three rats having wheat oil were not emaciated, and all appeared superficially to be in good health. No abnormal haemorrhage was noticed in any of the rats receiving either oil.

The incidence of uterine haemorrhage in relation to the vitamin A intake. In all these experiments on reproductive abnormalities uterine haemorrhage therefore only resulted when excess of vitamin A was given within 10 days after coitus. The incidence of haemorrhage in rats given oils within this period may be summarized:

Daily vitamin A intake (i.u.)	Incidence of uterine haemorrhage
40,000	0 out of 13
1,000	1 out of 11
0–200	0 out of 8

Haemorrhage in adult non-pregnant rats given excess of vitamin A. In the experiments on the effects of vitamin A acetate on pregnant rats, described in a preceding paragraph, haemorrhage in sites other than the uterus was observed in three instances. In two animals subcutaneous haemorrhages were found in the hind legs. A careful examination failed to reveal any corresponding lesion of the bones. The third rat apparently bled externally as the result of a minor injury caused by a lacerated scratching in the ear.

We have also observed haemorrhage in some male rats which for the purpose of another investigation had been given a diet deficient in vitamin E, with the subsequent addition of 36,000 i.u. of vitamin A in cod-liver oil. Only two out of six rats were affected. One died suddenly after receiving cod-liver oil for 17 days. There was no preceding loss in weight, and at autopsy normal intra-abdominal and subcutaneous fat deposits were found. The cause of death was massive haemorrhage ... the ... of which had ... and ... the ... and ... which, in addition to ... liver oil received adequate ... of ... and ... complete ... to ... after 18 days, ... without ... loss in weight. Post-mortem examination revealed haemorrhage in and around the bladder, in the pectoral muscles, and inside the cranial cavity at the base of the skull.

DISCUSSION

The lesions in hypervitaminosis A. The results described above indicate that vitamin A in the purest available form is toxic when given in great excess. It is improbable, however, that all the types of lesions which have been reported as the result of overdosing with crude concentrates are equally specific. Skeletal fractures and haemorrhages are, in our experience, the most characteristic lesions in genuine hypervitaminosis A. The fractures occur most consistently in young growing rats, and were found without exception in the present experiments. Haemorrhage is also frequent, if not invariable, in the fractured limbs. In adult rats the bones are probably more resistant to fractures, since we detected no breakages in our older animals. Haemorrhage, however, was frequent, although irregular in its incidence, distribution and severity. Bleeding was sometimes found in the limbs of rats which appeared to be in good health before they were killed. In others heavy internal haemorrhage into the viscera, or external haemorrhage through a minor wound, was rapidly fatal. The uterine haemorrhage in pregnant rats, originally described by Hartwell (1927), appears to be a special manifestation of the general liability to haemorrhage in hypervitaminosis A.

In many of our animals a rawness of the skin was often seen around the eyes, nose and mouth. This injury was undoubtedly due to overdosing with vitamin, but in view of the wide variety of oils which produce skin lesions it is to be considered a less specific lesion than fracture or haemorrhage. We have been unable to reproduce the fatal cramps which Matsuoka (1931) observed as the result of injecting vitamin A concentrates. He was, however, fully aware that the effect could be produced by substances other than vitamin A.

Hypervitaminosis A and scurvy. Mouriquand & Michel (1922) claimed that cod-liver oil antagonized vitamin A in guinea-pigs, causing scurvy even when lemon juice was given. Collett & Larkson (1938) supported this contention with regard to cod-liver oil, but found that a moderate excess of vitamins A and D had no injurious effect. Although normally the rat is not liable to scurvy, since it is able to synthesize ascorbic acid, Vedder & Rosenberg (1938)

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[illegible] that the symptoms [illegible] of vitamin A [illegible] Further experiments [illegible] Those [illegible] other sites. Our [illegible] bones the picture is [illegible] seen in scurvy. [illegible] Haemorrhages between the muscle planes are [illegible] in scurvy in adult human subjects, while similar haemorrhages are also frequent in experimental scurvy in the guinea-pig. Massive haemorrhages in the viscera, which often occurred in our adult rats, are less frequent in the human subject, but Ebbs & Hildorf (1941) state that 'bleeding may take place in any organ, and may vary in size from petechiae to huge extravasations.' Their report of a case of fatal haemorrhage into the peritoneum in a human subject recalls the observation of the same lesion in a hypervitaminotic rat by Bechdel & Moore (1933).

That young rats are more prone to bone fractures than older animals also recalls the greater predilection of skeletal lesions in infantile than in adult human scurvy. It must be noted, however, that in rats with hypervitaminosis fractures near to the centre of the shaft of the bone are the most prominent feature. The separation of the epiphysis, and fractures in the region near the growing end of the bone to which the human infant is particularly vulnerable, are sometimes present, but perhaps less conspicuous.

A detailed discussion of the points of similarity and difference between the gross lesions in hypervitaminosis A and in scurvy is made difficult by the variations which exist between the three modifications of scurvy as found in juvenile and adult human subjects and in the experimental guinea-pig. Even if we were to make the assumption that the symptoms in hypervitaminosis A are due to a conditioned form of scurvy, it would be too much to expect that the combination of lesions in the rat should either resemble one particular form of scurvy as found in another animal, or should include all the lesions which are found in all forms of scurvy. While, however, the anatomical resemblance between the lesions in hypervitaminosis A and in scurvy is in our opinion largely dependent on our interpretation of what the term 'scurvy' implies, we have been able to confirm the view that a secondary deficiency of vitamin C can be detected in hypervitaminosis A by biochemical means. Thus we were able, with pure vitamin A acetate either to repeat the observation of Vedder & Rosenberg (1938) that ascorbic acid affords protection against excess of vitamin A or to confirm, or to detect any alteration in the ascorbic acid content in rats fed on vitaminous rats.

Hypervitaminosis A and vitamins D and B. Hess & Lewis (1934) ascertained that vitamins A and D are antagonistic, and Gross & Sure (1935) have reported that bifocal dosing with vitamin A affords protection against many times the excess of vitamin D. The recent findings of Vedder & Rosenberg (1938) that vitamin D (100 i.u. daily) gives protection against excess of vitamin A concentrate is therefore not surprising. In our experiments, however, no benefit was derived from doses of 1 mg. of calciferol. In view of the toxicity of great excess of calciferol it may be necessary to adjust the dose carefully in order to provide protection against excess of vitamin A, and our findings must be taken to indicate only that no protection was exerted at the levels chosen. Additional allowances of the vitamin B complex have also been found to be beneficial to animals given excess of marine oils (Harris & Moore, 1928; Bell, Gregory & Drummond, 1933). According to Yamamoto (1934) and Yoshida (1937), however, the extra vitamin B complex, of which the active constituent is riboflavin, counteracts the injurious effect of higher unsaturated acids rather than of vitamin A. In the present experiment the effect of varying the allowance of the vitamin B complex was not investigated systematically, but such changes as were made from time to time had little or no obvious effect on the development of hypervitaminosis A.

SUMMARY

1. Hypervitaminosis A was induced in rats by giving them orally massive doses of either crystalline vitamin A acetate or halibut-liver oil.

2. The most characteristic lesions were skeletal fractures, which occurred most consistently in young animals, and internal or external haemorrhage. These injuries bore some superficial resemblance to those found in human and experimental scurvy.

3. The uterine haemorrhage in pregnant rats given excess of cod-liver oil, first reported by Hartwell, was reproduced in animals given excess of cod-liver oil, halibut-liver oil or vitamin A acetate. This haemorrhage appears to be a special manifestation of the general liability to haemorrhage in hypervitaminosis A.

Our thanks are due to Dr L. J. Harris for his valuable criticism, to British Drug Houses Ltd. for a generous gift of vitamin A acetate, to Prof. W. J. Hamilton of St Bartholomew's Hospital for histological examinations, to Miss A. C. Cooper and Miss J. E. Payne for the care of the experimental animals and to Mr A. W. Davies for X-ray photography. Y. L. Wang is indebted to the Medical Research Council for a personal grant.

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pected relative innocuousness and therapeutic ineffectiveness of mercurial diuretics in patients with renal disease may be related to the presence of marked proteinuria.

Addendum. After submission of this paper, we became aware of work done by Havill, Lichty, and Whipple,(21) showing that the tolerance of dogs for mercury bichloride was increased by frequent hemoglobin injections. It seems reasonable to assume that the mechanism of protection from the toxic action of the metallic ion was similar in this instance, since hemoglobin, like albumin, is reabsorbed by the proximal tubule cells until saturation of the reabsorptive capacity occurs, although Havill and his co-workers did not relate the protective effect to the occurrence of hemoglobinuria, which they did not measure, suggesting instead that the pigmented moiety of the hemoglobin molecule was responsible for the protection.

Summary. Administration of human albumin to rats, with resultant proteinuria, prior to administration of mercurial diuretics, sharply reduces renal toxicity of the mercurial. This effect is attributed to inhibition of mercurial reabsorption when the tubules are saturated with protein.

Simultaneous administration of human albumin and the mercurial enhances toxicity. This effect is attributed to the more rapid absorption of mercurial, concomitant with more rapid reabsorption of protein during the tubular loading phase.

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21. Havill, W. H., Lichty, J. A., Jr., and Whipple, G. H., *J. Exp. Med.*, 1932, v55, 627.

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Fetal Death and Maldevelopment Resulting from Maternal Vitamin A Deficiency in the Rat.* (17543)

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The course of pregnancy may be severely altered by feeding female rats a diet restricted in vitamin A, the severity of the alteration being roughly proportional to the degree of vitamin deprivation. Death and resorption of the fetuses, prolongation of pregnancy, and delivery of stillborn young were reported by Mason(1) and Cannon(2) who employed deficient diets with little or no supplement of vitamin A or carotene. Warkany and Schraffenberger(3,4) using similar diets supplemented with small amounts of carotene also noted a high incidence of fetal resorption; but, by interrupting pregnancy at various times from the 13th day to term, they were able to obtain a number of living and recently dead fetuses and newborns suitable for histologic study. The eyes of these offspring were found to bear several developmental anomalies, notably: folding and eversion of the retina, persistence of the choroidal fissure, absence of the ciliary body, and postlenticular fibroplasia. Thus, deficiency of vitamin A in the diet of female rats prior to and during pregnancy not only reduces fecundity by

* Supported by a grant from the Nutrition Foundation, Inc., New York.

1. Mason, K. E., *Am. J. Anat.*, 1935, v57, 303.

2. Cannon, M. D., PROC. SOC. EXP. BIOL. AND MED., 1940, v44, 129.

3. Warkany, J., and Schraffenberger, E., PROC. SOC. EXP. BIOL. AND MED., 1944, v57, 49.

4. Warkany, J., and Schraffenberger, E., *Arch. Ophthal.*, 1946, v35, 150.

causing fetal death and resorption, but also causes developmental anomalies in many of the fetuses that escape intrauterine death.

The widespread interest aroused by the success of Warkany and his collaborators in producing congenital malformations by means of maternal vitamin A deficiency makes it desirable that the work be repeated in another laboratory. To date the only published account of attempts to repeat the experiment elsewhere was that of Jackson and Kinsey,(5) who did obtain a few newborn rats with ocular malformations; but the positive results of this investigation were of such limited nature as to cast doubt on the facility and regularity with which such defective young might be produced. One of us (J.G.W.) has been associated with Dr. Warkany in a morphologic and embryologic study of the malformed fetuses and newborns obtained from the experiments carried out in Cincinnati. Since certain material needed for further investigation of this subject (placentae and early embryonic stages prepared especially for histochemical study) was not readily available from Dr. Warkany's laboratory, it was decided to produce it in this laboratory. The present report relates the repetition of the original experiment and, in addition, presents some observations not previously recorded.

Experimental. Vitamin A deficiency was induced and maintained by the same diets and experimental procedures as were employed in Warkany's original experiments,(3,4) except for the quantity and method of administration of the carotene supplement, and a few other matters of incidental nature specified below. Rats of two strains were used, the Albino Farms and the Wistar; the latter had not been used previously for this type of experiment. Since no difference in reaction to the experimental procedures was detected in animals from the different sources, the matter of strain will receive no further mention. A total of 36 young females were raised from weaning on a semipurified, "preparatory" diet which contained very little vitamin A or carotene. To insure continued growth to maturity a 15 microgram dose of carotene in olive oil was administered orally each week. Presumably this dosage did not permit appreciable storage of vitamin A. When the animals had attained a body weight of about 160 g, each female was given an opportunity to breed with a male of the same strain fed an adequate diet. If mating occurred, as indicated by presence of sperm in the vaginal smear, the female was transferred to a more highly purified diet which was adequate in all known respects except for the lack of vitamin A. No further supplemental dosing with carotene was given. The day on the morning of which sperm were found in the vaginal smear was considered the first day of pregnancy. Eight control females were fed the same diets and subjected to the same procedures but were given weekly supplements of 150 μg of carotene, both prior to and during pregnancy.

From the experience of other investigators,(1,2,6) it was expected that a large percentage of the pregnant females on vitamin A deficient diets would resorb all of their conceptuses at some time before term. On the other hand, Warkany and Roth(6) found that approximately 25% of the conceptuses which survived until the latter part of pregnancy were developmentally normal. The margin between fetal destruction and normal development, therefore, appears to be very narrow. One of the aims of the present experiment was to attempt to establish criteria by which one might predict ultimate destruction of the conceptuses, thereby making it possible to obtain prior to death embryos which were destined to undergo resorption later. Mason(1) observed that the presence of cornified cells in the vaginal smear during pregnancy was frequently associated with subsequent fetal death and resorption. Warkany and Schraffenberger(4) considered excessive amounts of blood in the vaginal smear and a loss of weight by the mother as indications that resorption had already begun. It was hoped that by carefully watching for all of these signs (cornified cells in the vaginal smear, excessive blood in the smear, and loss of weight

5. Jackson, B., and Kinsey, V. E., *Am. J. Ophthal.*, 1946, v29, 1236.

6. Warkany, J., and Roth, C. B., *J. Nutrition*, 1948, v35, 1.

Course	Age of fetuses when removed or delivered, days
	22
	22
	22
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TABLE I.
Course and Termination of Pregnancy in Vitamin A Deficient and Control Rats.

Age of fetuses when removed or delivered, days	Days of pregnancy on which untoward signs were observed: Cornified cells in smear (25% or more)	Abnormal blood in smear	Wt loss by mother	Condition of young: No. dead or resorb.	No. living	Mal-formed
22	—	—	19	0	11	No
22	—	—	—	2	7	Yes
22	—	—	11	2	8	Yes
20	6–16, 18, 20	18, 20	14	all		
19	7–14, 17, 18	10, 11, 16, 19	—	3	6	Yes
19	—	19	14	4	8	Yes
19	19	15, 17, 18	15, 18, 19	all		
19	7–18	10, 11, 19	15, 16	all		
18	4–11, 13, 14, 17, 18	15, 17, 18	13	all		
17	—	15, 16, 17	12, 13, 15	7	5	Yes
16	13–16	15	12, 14	all		
16	8, 10, 11	11, 15	14, 15, 16	all		
15	8–15	15	—	all		
15	1–13	11	14, 15	all		
15	9–11, 13	15	11	all		
15	4, 9, 14	15	13, 15	5	5	Yes
Controls						
22	—	—	12	3	9	No
22	—	15, 16	—	0	3	No
22	13, 14	17–20	13	4	4	No
22	—	—	—	0	14	No
22	—	—	—	0	7	No
20	—	—	—	1	13	No
17	—	—	13	0	11	No

by the mother) the future course of pregnancy might be determined with some degree of accuracy.

Fetal death. Of the 36 females raised until maturity on the preparatory diet 34 mated as indicated by sperm in the vaginal smear, but only 30 were later verified to have become pregnant. The first 16 pregnancies, after being transferred to the more highly purified diet, were allowed to continue to term or until there was definite evidence of prior resorption of some of the fetuses. Thus, this group provided a check on the reliability of the proposed criteria to be used in predicting intra-uterine destruction of the fetuses. Only 3 of these 16 pregnancies were sufficiently uneventful that they were allowed to proceed to the 22nd day of gestation (Table I). Thirteen were interrupted earlier by killing the mother when it was judged unlikely that any of the conceptuses would survive until term. Such judgment was made after at least two, and usually all, of the following signs became positive: 1) 25% or more of cornified cells in the vaginal smear during pregnancy; 2) blood in the vaginal smear in excess of, or at times other than, that characteristic of the "placental sign", which appears normally as a trace between the 11th and 15th days; and 3) a loss of weight by the mother, particularly after the 10th day.

It is apparent from the data in Table I that these criteria were of value in indicating the fate of the fetuses. In the absence of cornified cells and abnormal quantities of blood in the vaginal smear, a majority of the fetuses may be expected to survive until the 22nd day, as was observed in 3 vitamin A deficient and a large percentage of the control mothers. Conversely, cornified cells, to the extent of 25% or more were observed at one time or another in 11 of 13 females whose pregnancy was later interrupted. All fetuses in 9 and several in the remaining 2 pregnancies were dead or already undergoing resorption. Two A deficient females, whose pregnancy was interrupted for other reasons, failed to show as much as 25% of cornified

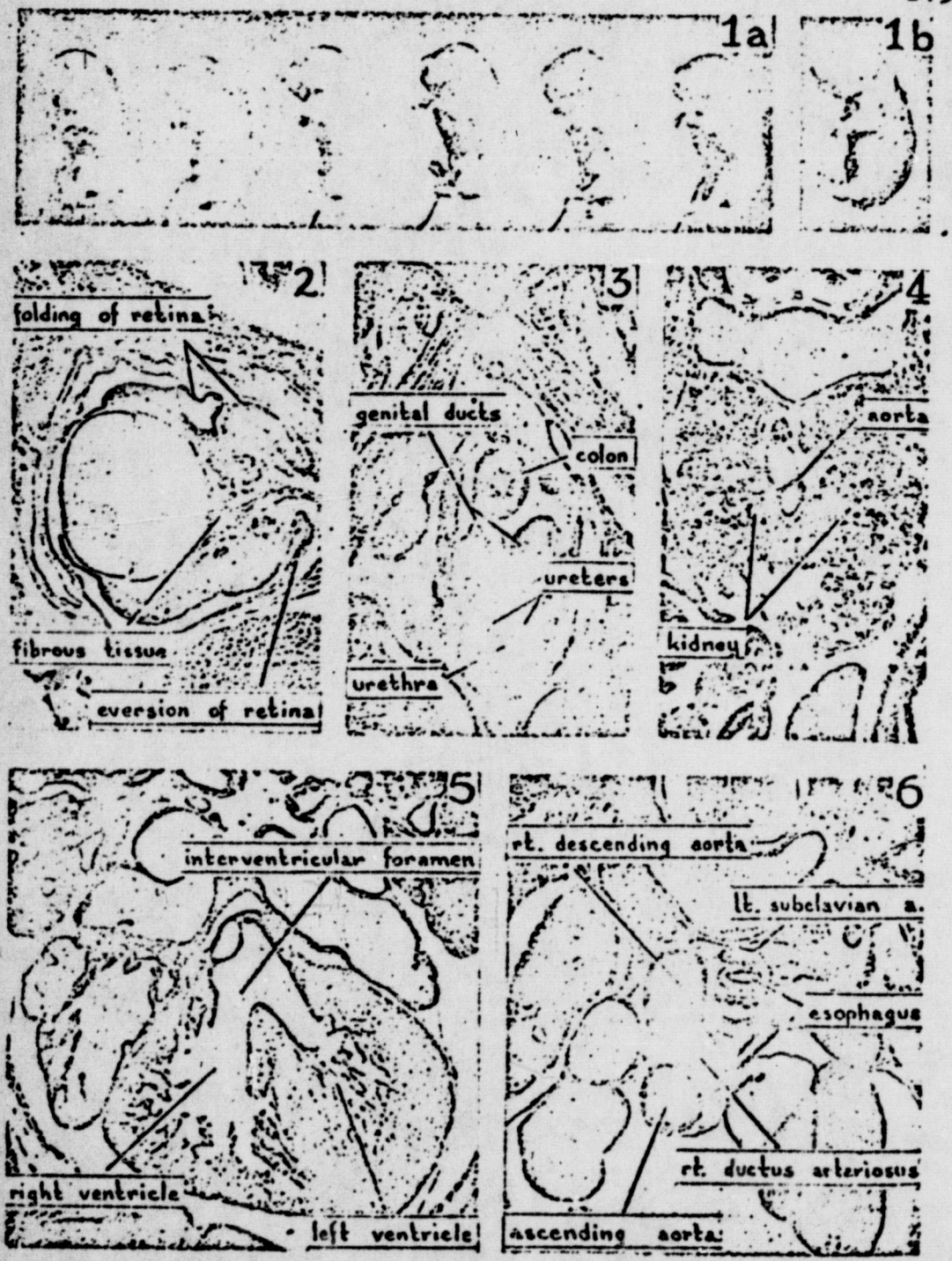

FIG. 1. a. Varying degrees of edema in young rats removed on the 22nd day of gestation from a mother fed vitamin A deficient diets. b. A normal newborn rat from a mother fed vitamin A deficient diets but supplemented with 150 μg of carotene per week.

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FIG. 2. Abnormal eye of a 22-day rat fetus, from a vitamin A deficient mother. The nervous layer of the retina is deeply folded, contains cysts, and is everted on to the pigmented layer in the region of the optic stalk and along the persistent choroid fissure. The vitreous chamber is reduced to a small cone-shaped volume which is filled with fibrous connective tissue and remnants of the hyaloid artery. Retinal coloboma was present but is not apparent in this section. × 25.

FIG. 3. Ectopic openings of ureters in a 19-day rat fetus from an A deficient mother. The left ureter is seen to terminate in the urethra, at some distance below its usual termination at the base of the bladder (normally attained by the 17th day). The right ureter emptied at an even lower level in the urethra. × 25.

FIG. 4. Horseshoe kidney in a 19-day rat fetus from an A deficient mother. × 25.

FIG. 5. Persisting interventricular foramen in the heart of a 19-day rat fetus from an A deficient mother. The foramen is normally closed by the 17th day of gestation. × 25.

FIG. 6. Right-sided aorta and right-sided ductus arteriosus in a 19-day rat fetus from an A deficient mother. The left subclavian artery is also anomalous in that it arises from the descending aorta and passes behind the esophagus to reach the left shoulder. × 25.

cells at any time during pregnancy; and both yielded some living young.

Blood in the vaginal smear, in excess of or at times other than that seen during the placental sign, was noted in all of the pregnancies which were later interrupted (Table I). This would seem to be in itself an excellent indicator of fetal destruction, were it not for the fact that a subjective estimate of the quantity of blood is necessary when it appears at the same time as the placental sign. A further limitation of this criterion was noted in that, prior to the 15th day, death and partial resorption of all fetuses often occurred before excessive blood was present in the vagina. On the other hand, when resorption of some conceptuses began during the last third of pregnancy, the quantity of abnormal blood was roughly proportional to the extent of fetal destruction. Two controls showed what was judged to be abnormal blood, and in both cases there was evidence that resorption of some fetuses had begun late in pregnancy.

Loss of weight in the mother was recorded for all but 2 of the pregnancies interrupted prematurely. Also, it was observed in 3 of the controls. The degree of loss was of more significance than the mere fact that a female failed to gain weight. Both the degree and rate of loss appeared to be determined by the number of fetuses undergoing resorption at any one time, as well as by the size of the fetuses at the time of their death.

Thus, of the 3 criteria used in following the course of pregnancy in vitamin A deficient females, no one was found to entirely reliable as an indicator of fetal destruction. However, when all 3 of these signs became positive during pregnancy, several if not all of the fetuses of that pregnancy were later found to have undergone intra-uterine destruction. Pregnancies interrupted after the appearance of only 2 of the criteria, despite the fact that they were not interrupted immediately, generally yielded some living young.

In an additional group of 14 vitamin A deficient females (not included in Table I) pregnancy was interrupted immediately when the second of any 2 of the signs described above became positive. Accordingly, all of these were killed between the 11th and 15th days. Of this group, 12 females yielded intact embryos, and all but one of these contained more intact than resorbed embryos. This procedure, therefore, proved successful as a means of recognizing impending destruction of the conceptuses, thereby providing embryos and placentae which, although doubtless affected by maternal vitamin A deficiency, had not yet begun disintegration. This material is being prepared for histologic and histo-chemical study of the early stages of abnormality in the embryos and of possible associated changes in the placentae.

Malformation of the surviving fetuses. Nineteen of the vitamin A deficient females mentioned in the preceding section yielded offspring suitable for histologic study, but only the fetuses of 15 days gestational age or older have yet been examined for malformations. Of the 7 "litters" comprising the latter group (Table I), all but one contained malformed fetuses. The one litter of normal offspring was from one of the 3 pregnancies which proceeded to term without appreciable indica-

tions of fetal destruction. No malformations or other abnormalities were found in the offspring of the control animals, which were fed the same diets and subjected to the same procedures as the A deficient mothers except that the controls were given 150 micrograms of carotene per week, both prior to and during pregnancy.

From the 6 abnormal litters older than the 14th day, at least 2 and in most cases all of the young have been serially sectioned and studied. Abnormality of the older fetuses was evident before sectioning by external appearance alone: the characteristic edema of head, neck and thorax was apparent to a variable degree in all (Fig. 1 a and b). Hemorrhage in the region of the eye and prenatal opening of the lids were occasionally noted.

Warkany and collaborators(7) have reported that ocular abnormality was the most prevalent type of developmental defect resulting from material vitamin A deficiency. This was substantiated by microscopic study of animals from the 6 abnormal litters listed in Table I. All such animals examined had ocular anomalies, the more common of which were: folding and eversion of the retina, presence of a mass of fibrous connective tissue in the much reduced vitreous chamber, persistence of the choroidal fissure (coloboma), and absence of the ciliary body (Fig. 2).

Genito-urinary organs also were frequently found to be the sites of malformation in earlier observations.(8) The same types of defects have again been encountered in a similar percentage of animals. Among the commoner abnormalities in both instances were hypoplasia of renal parenchyma, renal ectopia, ectopic ureteric openings (Fig. 3), incomplete development of Müllerian ducts, abnormal retention of heterologous genital ducts in both sexes, aplasia of vagina and faulty differentiation of the urogenital sinus. Less frequent abnormalities were horseshoe kidneys (Fig. 4), cryptorchidism, hypospadias, and atresia of genital ducts and ureters.

Cardiovascular anomalies were found in 44% of a selected group of fetuses and newborns from vitamin A deficient mothers in a previous study.(9) In the present, somewhat smaller group of animals an even higher incidence (more than 60%) of malformations of the heart and major arteries was observed. In general, the anomalies were of the same type, but a few varieties not previously seen were encountered. Failure of the interventricular septum to close was again the most common defect of the heart (Fig. 5). Variations in the aortic-arch pattern frequently observed in both instances were: distally-arising right subclavian artery, right-sided arch of aorta (Fig. 6), double arch of aorta, absence of 4th arch, absence or bilateral persistence of the ductus arteriosus, and absence of a pulmonary artery.

The occurrence of keratinizing metaplasia in epithelia of the lower genito-urinary tract of the offspring from A deficient mothers has been interpreted as indicating that such offspring had themselves experienced *in utero* a state of deficiency similar to that in the mother.(10) The same interpretation may be applied to the present group of animals, in which metaplastic keratinization was again observed in the genito-urinary tract of fetuses older than 18 days gestational age.

Summary. This report constitutes a confirmation of the original experiments of Warkany and co-workers in which congenital malformations were induced in fetal and newborn rats by maintaining the mothers on vitamin A deficient diets. In addition, a method has been standardized which permits prior recognition of imminent death and resorption of the conceptuses, thereby making it possible to collect many severely malformed fetuses that would otherwise be destroyed *in utero*. Three criteria that proved reliable in anticipating prenatal destruction of fetuses were: 1) the presence of more than 25% of cornified cells in the vaginal smear at any time during pregnancy; 2) the presence of blood in the vaginal smear in excess of or at times other than that

7. Warkany, J., Roth, C. B., and Wilson, J. G., *Pediatrics*, 1948, v1, 462.

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comprising the usual placental sign; and 3) a loss of weight by the mother after the 10th day of pregnancy.

Malformations involving the eye, cardiovascular system, and genito-urinary tract were found in the fetuses or newborns from all but one of the pregnancies from which intact offspring were obtained after the 14th day of gestation.

Received October 26, 1949. P.S.E.B.M., 1949, v72.

Beef Erythrocyte Extracts Reacting with Hemagglutinins in Infectious Mononucleosis and in Horse Serum Sickness. (17544)

H. SCHWARZWEISS* AND J. TOMCSIK

From the Hygienic Institute, University of Basel.

In previous publications(1,2) it was demonstrated that 2 serologically active substances can be isolated from the stroma of beef erythrocytes; one reacts with the hemagglutinins that are formed in infectious mononucleosis, the other, with those formed in horse serum sickness. The stroma of beef erythrocytes was first exhaustively extracted with acetone and then with 100% ethanol at room temperature, thus removing serologically inactive substances to a large extent. In order to isolate the specific reactants the stroma residue was then extracted with boiling 100% ethanol, and subsequently, with boiling 80% ethanol. As can be seen from Table I, the 80% ethanol extract yields the so-called mononucleosis antigen (M.A.) and the extract obtained with boiling 100% ethanol, the so-called serum sickness antigen (S.S.A.). Complete and distinct separation of the two serologically active substances could not be accomplished. The fractions do not correspond to pure haptens. However, on the basis of serological activity it could be assumed that the individual fractions were only 2-6% contaminated by the heterogenic fractions. Since the individual fractions are serologically highly active it was thought probable that they might demonstrate significant chemical differences which might point to the nature of the individual haptens. On the basis of previous investigations the nature of these haptens was disclosed only to the extent that they were found to be thermostable, not digestible by trypsin and pepsin, and did not give reactions characteristic for proteins. This report deals with the chemical analysis of the serologically active fractions of the beef erythrocytes. In addition, the glucose and glucosamine content after hydrolysis is presented.

Methods. 1. The C-, H- and N- determinations were done according to Pregl's method of quantitative elementary microanalysis.

2. Phosphorus was determined as ammoniumphosphomolybdate.

3. The reducing power was determined according to the Hagedorn-Jensen method and calculated for the glucose equivalent. The fractions were hydrolyzed at 100°C with 2 N HCl for 2 hours, then neutralized.

4. The glucosamine determination was done according to the method of Boyer and Fuerth as modified by Brunius.(3) 25-75 mg of dry substance were suspended in 7.5 ml of 4 N HCl and diluted with distilled water to 10 ml. This was hydrolyzed at 100°C in a sealed test tube for 5 hours. After filtration, whenever necessary, color clarification was effected by charcoal adsorption. This solution was carried to dryness over KOH and redissolved in 2 ml of distilled water. This, after

* This work was carried out by grant in aid from the Roche Research Fund, Basel, Switzerland.

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NORSK POLARINSTITUTT
(Formerly Norges Svalbard- og Ishavs-undersøkelser)

SKRIFTER

Nr. 95

HYPERVITAMINOSIS A

A STUDY OF THE EFFECT OF EXCESS OF VITAMIN A IN EXPERIMENTAL ANIMALS

Hypersensitivity
Page IV

BY
KÅRE RODAHL

OSLO
I KOMMISJON HOS JACOB DYBWAD
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vitamin C can be detected in hypervitaminosis A by biochemical means. Thus they were unable with pure vitamin A acetate, either to repeat the observation of Vedder and Rosenberg (1938) that ascorbic acid affords protection against excess of vitamin A concentrate, or to detect any abnormalities in the ascorbic acid metabolism in hypervitaminotic rats. Walker, Eylenburg and Moore (1947) reexamined the effect of vitamin C on hypervitaminotic rats, and found that the ascorbic acid gave no protection against either hemorrhages or fractures.

With regard to the mechanism of the intoxication of vitamin A, very little is known. Moore and his collaborators conclude that it is due to too rapid absorption of vitamin A and not to direct toxic effect of large stores of vitamin A in the liver. In Walker, Eylenburg and Moore's experiments on rats, examination of the vitamin A content of the plasma failed to reveal any definite level of the vitamin A in the blood associated with distinct symptoms of hypervitaminosis A. Josephs (1944) concludes that experimental and clinical observations indicate the existance of a mechanism for the maintenance of a constant level of vitamin A in the blood, possibly related to the activity of the reticuloendothelial cells. He states that the occurrence of hypervitaminosis A in a child reported by him indicates either that some defect existed in the system responsible for the protective reaction, or else that intense prolonged overdosage is capable of injuring the regularity mechanism. He also suggests that it is not the total amount of vitamin A in the body that determines the presence of toxic symptoms, but the ingestion of amounts large enough to overwhelm the ability of the liver to remove it from the circulation.

2. Hypervitaminosis A in Man.

Little is known about the toxic effect of excess of vitamin A in man. Rodahl and Moore (1943), from chemical and biological investigations of the livers of polar bears (Ursus maritimus), and bearded seals (Erignathus barbatus) came to the conclusion that the illness which may promptly follow from eating these livers is due to intoxication from the huge amounts of vitamin A which they contain, since a consumption of about three-quarters of a pound would provide 7,500,000 I. U. vitamin A which, on analogy with rats, would be a toxic quantity. The symptoms of this acute polar bear liver poisoning, which may start within two to four hours, are drowsiness, sluggishness, irritability or an irresistible desire to sleep, severe headache and vomiting. In severe cases peeling of the skin around the mouth appears after twenty-four hours and may remain confined to the face, or the whole skin from head to foot may be involved.

In a more comprehensive study of the toxic effect of polar bear liver, Rodahl (1949, 1, 2,) confirming this conclusion, found that the livers

of Arctic mammals, which are known by the Eskimos to be poisonous, such as polar bear, bearded seal and Greenland fox, were very rich in vitamin A, while the livers of snow hare and walrus, which are considered non-poisonous by the Eskimos, contained only small amounts of vitamin A. In experiments on rats the toxic substance of bear liver was found to be identical with vitamin A, and ingestion of large quantities of bear liver led to the condition of hypervitaminosis A. The clinical symptoms of acute intoxication observed in rats following the ingestion of large single doses of vitamin A could well be compared with the symptoms observed in man following a single meal of bear or seal liver.

Rodahl and Moore (1943) also mentioned a man who took about 6,000,000 I. U. vitamin A daily for five days, in the form of halibut liver oil. He became severely ill, the main symptom being giddiness. The patient recovered within ten days after the ingestion of the halibut liver oil had been discontinued.

Some workers have reported that comparatively small doses of vitamin A may give rise to toxic symptoms in man. Thus Getz et al. (1939) reports that 2,000,000 I. U. vit. A in a single dose may give a dull headache, and Spiesman (1941) has seen adults who suffer from general malady with loss of weight and appetite on only 14,000 I. U. daily. On the other hand, others (Bicknell and Prescott (1947)) have given 144,000 I. U. daily for many weeks with no ill effects apart from an occasional transient diuresis at the beginning of the treatment. In children doses of 300,000 I. U. daily for several weeks or several months appeared to be harmless (Lehman and Rapaport (1940)).

Prolonged administration of vitamin A in large amounts may, on the other hand, be dangerous. Thus Josephs (1944) has reported a case of severe hypervitaminosis A in a three years old boy, who from the age of two or three months was given one teaspoon of halibut-liver oil daily, corresponding to approximately 240,000 U. S. P. units of vitamin A. It was found that his height was normal for his age, but his scalp hair was scarce, dry and coarse, and he had no hair on his body, nor had he any eyebrows. The condition was characterised by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development and clubbing of the fingers. The erythrocytes sedimentation rate was 6 mm in one hour on one occasion, and 0 on two others. Roentgenograms of the chest and skull showed no abnormalities, but those of the limbs revealed considerable irregularity of the cortical structure. In the phalanges and metacarpals the cortex was extremely thin and the epiphyses of the upper end of the humeri and tibiae were mottled in appearance. It was found that when the extra supply of vitamin A was removed, the improvement was immediate. Within two months the appetite had improved, the patient had gained weight and his hair had begun to grow quite normally.

It is probable that the observed spectral structures are to be classed as hyperfine—they arise from interactions between the magnetic moments of the nitrogen and hydrogen nuclei in each molecule with the magnetic moment of the odd electron. Despite the complexity and breadth of the spectra of their dilute solutions, the crystals of the nitro-free radicals exhibit a single sharp line.[6] The trinitrofluorenone derivative yields a rather broad, unresolved resonance peak. It is possible that the fine structure in this case, as in the case of many other free radicals, is unresolved because of its complexity. This complexity arises from the large number of nuclear moments with which the electronic moment interacts.

Although the fact that sodium metal catalyzes the polymerization of unsaturated compounds has been known for a long time, there is no general agreement concerning the mechanism of this catalysis (*8*). Two sets of experiments have been performed with styrene which indicate that the function of the sodium metal is to bring about the formation of a negative hydrocarbon free radical. This free radical ion then initiates the chain reaction involved in the polymerization, as suggested by Bolland (*9*) for the sodium-catalyzed polymerization of isoprene. In one experiment a small amount of sodium dispersion was added to a sample of styrene. After some hours the styrene had been converted to a deep-red, rubbery solid which showed a strong paramagnetic resonance absorption. It is believed that the red color and the paramagnetic absorption are due to species such as $(C_6H_5CH{-}CH_2)^-$ which were trapped in the polymer. The material retained its paramagnetic resonance absorption and its color over a period of several months.[6] In other experiments, styrene was dissolved in 1,2-dimethoxyethane and a small amount of sodium dispersion was added. A very vigorous reaction set in immediately, accompanied by the formation of a deep-orange color. As the reaction subsided, the reaction mixture became very viscous and the orange color gradually faded away. Since 1,2-dimethoxyethane, as mentioned above, favors the formation of negative hydrocarbon free radicals, it is believed that these observations are further evidence that the actual polymerization catalyst is a species such as $(C_6H_5CH{-}CH_2)^-$.

Various investigators have suggested (*10*) that abnormal growth may be explained by a free radical mechanism. Perhaps the carcinogenic activity of 20-methylcholanthrene and 1,2-benzanthracene is due to their ability to form negative hydrocarbon free radicals with mild reducing agents, whereas noncarcinogenic hydrocarbons such as naphthalene and anthracene are able to form such free radicals only with very strong reducing agents.[7]

[5] A similar phenomenon was first observed in diphenylpicrylhydrazyl, dilute solutions of which have been found by Hutchison, Pastor, and Kowalsky (*J. Chem. Phys.*, 20, 534 (1952)) to show hyperfine structure covering about 50 oersteds. The crystals, on the other hand, show a single sharp line about 2 oersteds wide.

[6] It should be noted that this experiment is not readily reproducible. In view of the competition between the formation of the catalytic species, $(C_6H_5CH{=}CH_2)^-$, and the many processes by which it may disappear, it is not surprising that the magnetic absorption phenomenon is difficult to reproduce.

Manuscript received September 15, 1952.

[7] A study of the relative electron affinity of various hydrocarbons is in progress in this laboratory.

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Excessive Intake of Vitamin A as a Cause of Congenital Anomalies in the Rat[1]

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Congenital anomalies have been produced in animal young when the fetal environment has been influenced by chemical, endocrine, mechanical, and actinic factors (*1*). Changes in atmospheric pressure (*2*) (hypoxia) and administration of cortisone (*3*) have recently been shown to exert teratogenic effects. Similarly, deficiencies in the maternal diet of single nutritional elements such as minerals (copper [*4*] and iodine [*5*]) and vitamins (riboflavin [*6*], pantothenic acid [*7*], folic acid [*8*], and vitamin A [*9, 10*]) have induced defective offspring. Reports (*11, 12*) of vitamin A excess in the maternal diet have shown a diminished litter rate and a high incidence of fetal resorption *in utero*. In the course of our investigation of the skeletal changes of hypervitaminosis A in mature rats, it was noted that several pregnant animals produced offspring with congenital malformations. An investigation was undertaken to study this phenomenon.

One hundred and fifty female rats of the CF Wistar strain (175-200 g) were mated by exposure for 24 hr, during the pre-oestrous stage, to males of the same strain. Pregnant females were fed the standard Rockland pellet diet and water *ad lib*. From the 2nd, 3rd, or 4th to the 16th day post coitus, 35,000 IU vitamin A in 0.7 ml diluent[2] were administered daily via stomach tube, to 100 animals in the experimental group.

[1] Aided by grants from the Legal League for Philanthropies, Inc., New York City, and Mead Johnson Co., Evansville, Ind.

[2] The vitamin product used was an aqueous preparation containing 50,000 USP u/cc natural vitamin A dispersed in sorethitan monolaurate and water.

Geneva, N.Y. 117
May 15, 1953

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TABLE 1

INCIDENCE OF CONGENITAL CRANIAL ANOMALY

Animal no.	No. of offspring in litter	No. with congenital cranial anomaly	Gestation days fed 35,000 IU vitamin A
14	10	4	2–16
30	6	4	4–16
35	6	4	4–16
39	6	1	4–16
59	9	5	3–16
62	11	3	3–16
79	9	9	2–16
90	2	2	2–16
93	5	5	2–16
100	8	2	2–16
Total	72	39 (54%)	

Fifty control animals were fed 0.7 ml of the diluent. The animals were sacrificed on the 20–21st day post coitus (at or near term), and each litter was examined for gross congenital defects. In both groups most of the young were alive when removed from the amniotic sac. All were placed in fixative solution for histologic study.

Excessive intake of vitamin A from the 2nd, 3rd, or 4th to the 16th day of gestation resulted in a marked reduction in the number of litters carried to term. Of 50 control mated females, 44 produced litters, with a total of 410 apparently normal newborn, a successful pregnancy rate of 88%; whereas of 100 mated females in the experimental group, only 10 carried young to term, with a total of 74 offspring, a successful pregnancy rate of 10%. This marked pregnancy failure rate is in accord with previous reports (*11, 12*).

The incidence of gross congenital defects in the litters carried to term in the experimental group is seen in Table 1. Of 74 offspring produced in 10 litters, 34 exhibited a gross anomaly in the development of the skull and brain, a deformity rate of 54%. In the control group no anomalies were noted in 410 offspring.

The gross developmental defect apparent in each of the abnormal offspring rats is an extrusion of the brain (Fig. 1) to the external surface of the head. There is a thin membranous covering over the exposed brain tissue. Sporadic anomalies noted were macroglossia, harelip, cleft palate, and gross defects in eye development. The cranial deformity, however, was a consistent finding. It is of interest that comparable cranial anomalies (as determined by photographic similarity) have been produced in mice by other teratogenic methods such as hypoxia (*2*) induced by exposure of the pregnant animal to atmospheric pressures of high altitudes, or by the translocation effect (*13*) in the second-generation offspring following irradiation of the initial sire male.

Results of this preliminary experiment indicate that the administration of excessive amounts of vitamin A to pregnant rats produces a diminished litter rate and characteristic malformations among the surviving young.

FIG. 1. *A*, lateral view of experimental and control rat at term. *B*, lateral close-up of experimental animal showing brain extruded to surface of head. Protruding tongue is abnormal. *C*, close-up view of extruded brain from above. Note longitudinal fissure of the cerebrum.

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EXCESSIVE VITAMIN A AND CONGENITAL ABNORMALITIES

Experimental studies have shown that a lack of vitamin A in the maternal diet during gestation results in widespread structural abnormalities in the young. Pregnant rats maintained on a vitamin A-deficient regimen have been reported to have fewer live young and an increased incidence of fetal reabsorption. Their young show an increased proportion of congenital defects in the visual, cardiovascular, or genitourinary systems.[1] Contrarywise, it has recently been found [2] that excessive intake of vitamin A also caused congenital defects to appear in offspring of mothers that received this supplement. One hundred fifty female rats were studied after being mated. One hundred received orally 35,000 I.U. of vitamin A per day from the 2nd, 3rd, or 4th to 15th day post coitus, while the 50 control animals received no extra vitamin. All animals were killed at, or near, term and the young examined for gross congenital defects.

In the control group, 44 of the 50 rats produced litters with a total of 410 apparently normal young being formed. Thus, 88% of the animals of the control group had successful pregnancies. On the other hand, of the 100 rats mated that received excess amounts of vitamin A, only 10 carried young to the end of the study (10% successful pregnancies). Thus, 58% of the animals whose mothers received excessive amounts of vitamin A showed congenital defects, while no congenital defects were observed in the control group. Cranial deformities were found constantly in the young of the test group. In this deformity there was an extrusion of the brain to the external surfaces of the head, with a membranous film covering the exposed brain surface. In addition to the skull deformity, other congenital defects were also noted sporadically, such as harelip, cleft palate, and defects in eye development.

These studies indicate that ingestion of excessive amounts of vitamin A by pregnant animals as well as severe restriction of this dietary factor produces severely deliterious developmental effects, an observation which suggests that there is an optimal range of vitamin A dosage just as there is for other dietary essentials.

BRUCELLOSIS

In the last two years notable advances have been made in our knowledge of brucellosis, and this has been presented in a technical report from the World Health Organization.[1] Infection with Brucella abortus may remain inapparent or subclinical or it may become manifest as an acute febrile disease of limited duration or a long-continued disease with periodic exacerbations. A positive culture is the only sure criterion of the presence of the disease. This may be from the blood, bone marrow, a recently enlarged lymph node, the cerebrospinal fluid, urine, or discharge from an abscess. Other diagnostic aids are (1) the sero-agglutination test, which when carried out with a suitable antigen and satisfactory technique almost always gives a significant positive result in the presence of active infection (positive reactions of low titer should be rechecked); (2) the complement-fixation test, which, although used by some, is believed by the Expert Committee to have no practical value; (3) the opsonocytophagic test, which the committee also regards as unsuitable for diagnostic use despite the fact that it has its adherents; (4) the intradermal test, which when positive unfortunately denotes only that the patient has had previous contact with Br. abortus but does not indicate active infection; and (5) a normal leukocyte count or leukopenia with or without a relative lymphocytosis in a febrile patient, which while not pathognomonic is nevertheless suggestive of brucellosis and should lead to the taking of cultures.

Of all the possible sources of culture material Spink and his co-workers [2] believe that sternal marrow yields the greatest percentage of positive results. The special culture mediums now available are considered superior to guinea pig inoculation. These authors find the agglutination test of special value in patients who have been empirically treated with antibiotics with the result that cultures are negative, but they warn that there is a wide variation in the reliability of antigens and that false positive results may occur as a result of cross agglutination in patients with tularemia or patients who have been immunized against cholera.

Elsewhere in this issue Spink and Thompson (page 1162) report two cases of human infection with Br.

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DISTURBANCE OF EMBRYONIC DEVELOPMENT BY MATERNAL VITAMIN DEFICIENCIES[1]

JOSEF WARKANY

The Children's Hospital Research Foundation,' Cincinnati, Ohio

SEVEN FIGURES

The topic to be discussed represents but a small sector of the field of prenatal nutrition. Even the sector circumscribed by the title of this paper has grown too large to be covered completely in this conference. It will be necessary, therefore, to limit this presentation to certain phases of the work which demonstrate the role of vitamins in the development of mammalian embryos. Instead of aiming at completeness it seemed preferable to point out some of the ramifications of our subject which reach into other fields discussed in this symposium.

Many forms of reproductive failure may be caused by maternal vitamin deficiencies: sterility, fetal death, resorption or abortion, neonatal weakness or death of the offspring are probably the most frequent results of maternal dietary deficiency; they are results of practical importance in animal as well as in human reproduction. "Malformations" were omitted from this list since they can occur at any stage of development and play a part in many forms of reproductive failure. Under adverse conditions few deformed fetuses reach the natal period and "congenital" malformations are, therefore, relatively rare manifestations of maternal dietary deficiency. They occur in exceptional cases as the result of borderline deficiencies which injure the developing embryo but permit continuation of pregnancy. Mitigation of a bor-

[1] The work from this institute was supported in part by grants from The Nutrition Foundation, Inc., New York, N. Y.

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derline deficiency leads, as a rule, to the birth of normal young, but further deprivation leads to embryonic death (Warkany, '47). It is difficult, therefore, to obtain congenital malformations of dietary origin. The investigator who tries to produce such malformations resembles a tightrope walker who is constantly in danger of falling to one side or the other. It is understandable that failure and disappointments are not rare in this field; yet the results are of considerable interest, since they permit an insight into embryonic development which cannot be obtained by other methods. An attempt will be made to justify this statement by the following examples.

Reproductive failure owing to vitamin A deficiency has been studied by many investigators (Evans and Bishop, '22; Mason, '35). In the course of such studies congenital anomalies have been observed occasionally (Zilva *et al.*, '21; Moore, '39). But it was Hale ('33, '35, '37) who first furnished convincing proof that congenital malformations can be induced in pigs by maternal vitamin A deficiency. This investigator fed gilts of known stock a diet deficient in vitamin A and possibly in other nutritional factors. The offspring showed microphthalmus or anophthalmos, accessory ears, cleft palate and harelip, subcutaneous cysts, and ectopic kidneys. Hale proved the nutritional origin of these malformations by preventing them in control animals when the experimental diet was supplemented with cod liver oil or green fodder. He also proved that genetic factors could be ruled out as the cause of the malformations, since matings of abnormal sons to their mothers or of abnormal brothers to their abnormal sisters resulted in normal offspring if the females were fed an adequate diet during pregnancy. A different type of congenital blindness caused by bony constriction of the optic nerve and attributable to carotene deficiency of the mother was reported in calves by Moore and coworkers ('35). Extensive studies along these lines were made possible when we found that congenital malformations could be induced in rats by maternal vitamin A deficiency (Warkany and Schraffenberger, '46). The diet of

the prospective mother must be controlled soon after weaning. By adding measured amounts of carotene to a vitamin A-free diet the females are enabled to grow and mature without storing vitamin A. The day after conception they are given a completely vitamin A-free diet. In this way young can be obtained which show a syndrome of congenital malformations. Externally, these young may appear normal but sometimes they are characterized by marked edema. The eye, which is one of the most frequently affected organs in this syndrome, shows a variety of anomalies (fig. 1 A) but in all abnormal eyes a fibrous retrolenticular membrane is found. The retina is often folded and of abnormal structure; there are many instances of coloboma and of eversion of the retina; the iris and the ciliary body are rudimentary; the cornea may be fused with the lids; and "open eyes" are observed in rare cases. Malformations of the urogenital tract follow next in frequency. In many animals the lower poles of the kidneys are close together and their pelves are not dilated. In more severely affected animals the lower poles of the kidneys may be fused and horseshoe kidneys are formed (fig. 1 B) (Warkany and Roth, '48). Serial sections revealed many additional anomalies of the urogenital system (Wilson and Warkany, '48). A high percentage of these young have diaphragmatic hernias, more often on the right than on the left side (fig. 1 C). The interventricular septum of the heart may remain open beyond the age of normal closure (fig. 1 D) and aortic arch anomalies of many types can be discovered in serial section (Wilson and Warkany, '49). In these experiments rats of several strains were used and the same types of malformations were induced by maternal vitamin A deficiency irrespective of the stock employed. Females of the same strains receiving adequate diet or the experimental diet supplemented by vitamin A did not have abnormal young (Warkany and Schraffenberger, '46; Wilson and Burch, '49).

Figure 2 A shows the incidence of anomalies in one representative group of abnormal young with the vitamin A-deficiency syndrome. In this experiment 53% of the young

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Fig. 1 Congenital anomalies in young of vitamin A-deficient female rats.

A. Section of abnormal eye (× 20) showing retrolenticular fibrous membrane in place of the vitreous body, coloboma and eversion of the retina, rudimentary iris, and ciliary body.

B. Section through abdomen (× 6), showing marked edema of subcutaneous tissue and fusion of hind joints of kidneys (horseshoe kidney).

C. Section through diaphragmatic area (× 6). The small dorsal lobe of the liver penetrates through a defect of the diaphragm into the right pleural cavity.

D. Section through heart (× 10). A blood clot (white arrows) is seen in septal defect.

Fig. 2 Percentage incidence of affected organs in abnormal young. Vitamin A deficiency of mothers maintained: A throughout gestation, B. through 14 days, C. through 12 days of gestation. Note change of pattern. (From Warkany, 1952-1953.)

were abnormal. Of these abnormals, over 90% had both ocular and urogenital anomalies, 58% had diaphragmatic hernia, while only 17% had cardiovascular malformations. This syndrome can be modified by interrupting the maternal dietary deficiency by administration of a single large dose of vitamin A on certain days of gestation. Vitamin A-depleted mothers were given the single vitamin A supplement on different days, some on the tenth, others on the eleventh, twelfth, thirteenth, fourteenth, and fifteenth day of gestation. It was found that the percentage of abnormal young became smaller the earlier the supplement was given. But it was also found that the prevalence of certain anomalies changed according to the date of vitamin A administration and that the pattern was affected. If, for instance, vitamin A was administered on the thirteenth day the ocular and urogenital anomalies were markedly reduced, while the incidence of cardiovascular anomalies was relatively increased (fig. 2C). The change of the syndrome can be explained in the following way. Vitamin A deficiency damages the heart and the aortic arch system before the thirteenth day, whereas the interference with the development of the corpus vitreum of the eye occurs later. The retrolenticular fibroplasia, but not the cardiac anomalies, can be prevented, therefore, by a supplement on the thirteenth day. In figure 2B an intermediate pattern is seen which was produced by vitamin A supplements on the fifteenth day. Thus the syndrome can be altered when vitamin A is administered during gestation (Warkany, '52-'53; Wilson *et al.*, '53).

The syndrome induced in the young of rats by maternal vitamin A deficiency consists essentially of malformations of soft tissues. A syndrome of skeletal malformations can be obtained by maternal riboflavin deficiency. Under proper experimental conditions about one third of the young born are found to be abnormal (Warkany and Nelson, '41; Warkany and Schraffenberger, '44). Many of the abnormal young can be recognized as such by external inspection. They show shortening of the mandible and of the extremities, protrusion

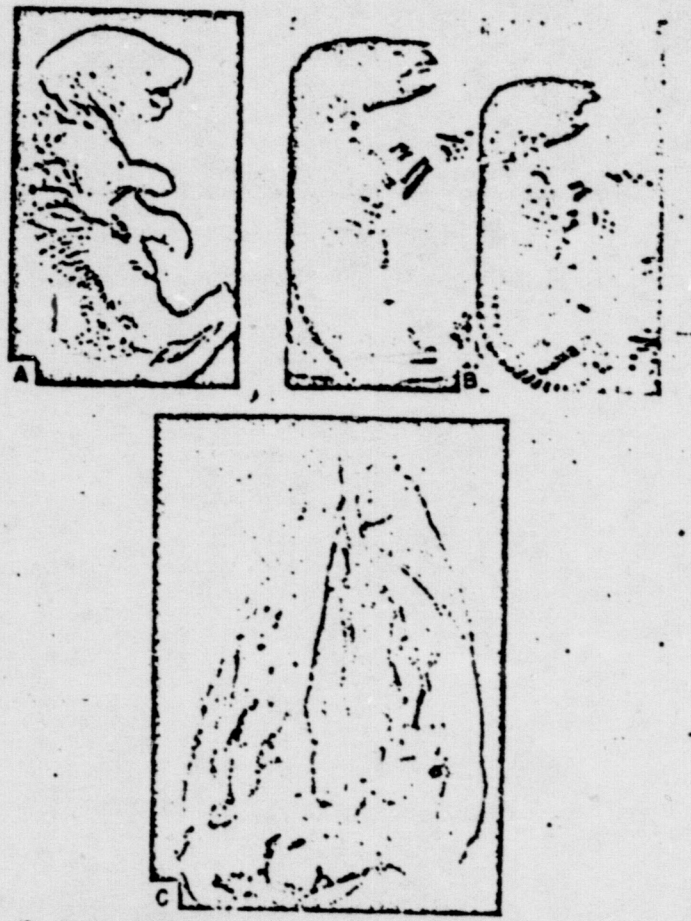

Fig. 2 Congenital anomalies in young of riboflavin-deficient female rats.

A. Young showing short mandible and protrusion of tongue.
B. Cleared specimens both showing shortening of mandible and fusion of ribs. In the right specimen there is shortening of the radius and ulna and absence of the tibia and fibula. In the left specimen the tibia appears absent and the fibula is curved.
C. Cleft palate.

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of the tongue and various degrees of syndactylism (fig. 3 A) (Giroud and Boisselot, '47; Giroud *et al.*, '51; Leimbach, '49; Nolnck and Kuppermann, '44; Piccioni and Bologna, '49). Other abnormalities are recognized after the specimens are cleared. There may be shortening or absence of the radius, ulna, tibia, and fibula. The mandible is often short and the ribs are fused (fig. 3 B). Inspection of the mouth reveals a posterior cleft palate in about one-half of the abnormal young (fig. 3 C) (Warkany *et al.*, '43b).

These young have different degrees of abnormality; but there is a pattern in this variety, in that certain bones are less often affected than others. Table 1 shows the frequency of osseous anomalies in 100 cleared abnormal specimens.

TABLE 1

Frequency of osseous defects in one hundred cleared abnormal specimens

Tibia	93	Ulna	50
Mandible	80	Humerus	34
Rib	73	Hindfoot	31
Fibula	63	Maxilla	8
Radius	56	Scapula	6
Hand	54	Clavicle	6
Sternum	32	Femur	1

Histologic sections of the abnormal bones reveal some interesting features (Warkany and Nelson, '42; Warkany *et al.*, '43a). A comparison of normal tibiae with abnormals shows retarded and irregular ossification in the specimens with malformations. In a mildly abnormal tibia the metaphyseal lines of ossification take an irregular and somewhat wavy course. Large cartilaginous areas remain enclosed within the diaphysis. The bone trabeculae radiate diagonally forward from a slightly elevated point in the center of the posterior aspect of the bones. A more abnormal tibia remains almost entirely cartilaginous although beginning ossification can be recognized in a posterior prominence of the structure. This prominence is covered by a thin shell of bone, but consists otherwise entirely of swollen cartilage cells. Anterior to these cells lies columnar cartilage, the cell columns radiating forward from the posterior bulge. A further degree of anomaly may be seen in a tibia which consists entirely of cartilage of the resting type (fig. 4).

Sections of the paws also show retarded and irregular ossification. In addition, a disorganization of the normal carpal and digital pattern may be recognized. Some bones are shortened or entirely lacking, others are wider than normal and some of the interosseous spaces and articulations are not developed (fig. 4). In some of the short tubular bones eccentric foci of ossification are seen.

It may be safely concluded from such histologic studies that the abnormal skeletal development dates back to the cartilaginous or to earlier stages of development. But it may not be learned from the sections how early in prenatal life the anomalies are determined. These studies were complemented, therefore, by experiments designed to reveal how late in the gestational period the malformations could be prevented by supplements of the deficient diet. It was found that addition of the supplement prevented all skeletal malformations of the young when the supplement was given before the thirteenth day[2] of gestation (Warkany, '52-'53). After the thirteenth day supplementation of the diet did not protect the young.

These findings suggest that riboflavin is needed for the development of the skeleton, particularly between the thirteenth and fourteenth days of embryogenesis. At this period the appendicular skeleton is still in its mesenchymal state, but its individual elements, the future bones and the joint spaces which separate them, have become recognizable. Between the thirteenth and fourteenth days of gestation the embryo is growing rapidly and is almost trebling its weight within a 24-hour period (Donaldson, '24). After this period the riboflavin deficiency does not interfere seriously with general growth and increase in weight, since malformed young

[2] In our experiments the first day of gestation is designated as the day on which sperm are found in the vaginal smear.

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Fig. 1 Sections through skeletal structures of young of riboflavin-deficient female rats.

A. Abnormal tibia (× 16) showing retarded and abnormal ossification. Islands of cartilage are seen in the anterior aspects of the diaphysis; the osseous trabeculae take a diagonal, abnormal course.

B. Tibia short and completely cartilaginous (× 21) in the presence of a fairly well ossified fibula. Note abnormal curving of the fibula around the shortened tibia (*cf.* fig. 3 B left).

C. Paw (× 26). Cartilaginous bridges connect distal ends of radius and ulna with carpal cartilages. Below a broad metacarpal bone (synostylism) is seen with eccentric center of ossification.

may be normal in size and weight at the time of birth. But the deficiency does prevent normal differentiation of the skeletal mesenchyme into cartilage, bone, and articular spaces. It seems, therefore, that at this active stage of development large amounts of riboflavin are required for normal differentiation.

To test whether our concept of this period of determination is correct we undertook in 1946 some collateral experiments using X rays as the teratogenic agent (Warkany and Schraffenberger, '47). It seems justifiable to mention here the results of that study, although they are only indirectly connected with the topic of this paper. As early as 1925 Job *et al.* ('25) employed X rays to determine critical periods in mammalian development and in 1928 Kaven ('28a, b) reported cerebral malformations after timed irradiation of pregnant mice. I wish to emphasize this fact, since some recent students (Hicks, '53) in this field have apparently overlooked the earlier work along these lines. If the time of injury to the embryo had the overwhelming importance for the morphology of malformations as the work of Stockard ('21) suggests, it should be possible to produce the same type of skeletal malformation by riboflavin deficiency and by X-irradiating between the thirteenth and fourteenth days. On superficial examination, the results of this test seemed rather gratifying, since some of the malformations produced by irradiation resembled externally those induced by riboflavin deficiency. Shortness of the lower jaw, protrusion of the tongue, cleft palate, shortness of the extremities, abduction of the hands, clubfeet, and syndactylism were malformations common to both syndromes (fig. 3). But there were many differences between the two types, the X-ray syndrome being much more varied than that induced by riboflavin deficiency. By irradiation on the thirteenth day a number of young were obtained which had encephaloceles or polydactylism, anomalies not observed in the riboflavin-deficiency syndrome. Characteristic differences were recognized after the specimens were cleared. Specimens of the two types which appeared similar

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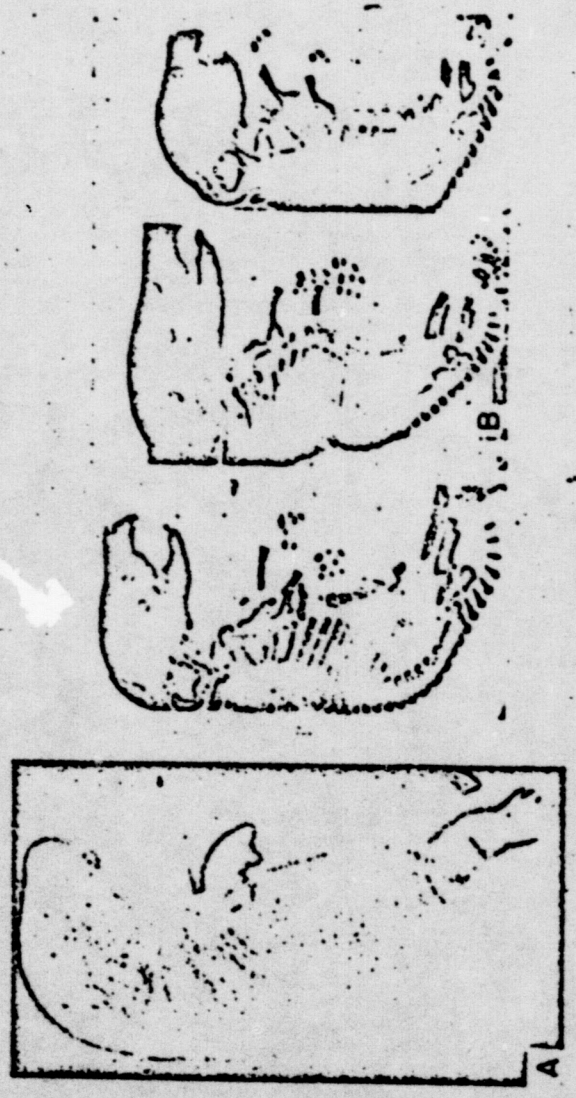

Figure 5

A. Young of female rat irradiated on thirteenth day of pregnancy (30×). Note shortness of mandible, protruding tongue, syndactylism, and malposition of extremities.

B. Control specimen; young of female rats irradiated on the thirteenth day of pregnancy (32×). Left: Shortness of mandible, humeroradial bone, shortness of ulna. Center: Humeroradial bone, absence of ulna, shortness of femur and fibula. Right: Shortness of mandible, humeroradial bone, absence of ulna and fibula.

externally could be easily distinguished by differences of the skeletal structures. In the pattern produced by irradiation on the thirteenth day both the ramus and the corpus mandibulae were reduced in size and both the ulna and the fibula were more shortened than the radius and the tibia. There was also a frequent occurrence of a humeroradial bone which was never observed in several hundred abnormal specimens obtained from riboflavin-deficient mothers. In the pattern of riboflavin deficiency, the shortening of the mandible was due to a reduction in size of the corpus mandibulae; the ramus was of normal size. The radius and the tibia were usually more shortened than the ulna and the fibula. Histologic sections revealed further differences. In the irradiation syndrome sections of an arm with osseous ankylosis of the humerus and radius showed absence of the distal epiphysis of the humerus and of the proximal epiphysis of the radius, the osseous trabeculae of the two bones being connected without demarcation (fig. 6). Sections of the brain and other internal organs (fig. 7) showed anomalies not seen in the pattern of riboflavin deficiency (Russell, '50; Wilson and Karr, '51; Wilson *et al.*, '53). Comparison of the two syndromes permits the following conclusions: It is probably correct that the riboflavin deficiency exerts its deleterious influence about the time of the thirteenth day of gestation. But, as would be expected in a chronic teratogenic experiment, the time of determination cannot be exactly defined. Another conclusion is that the time element must not be overemphasized to the neglect of other factors, since specific injurious agents influence development in specific ways. Although similar anomalies can be produced by different teratogenic factors, variances can be found on thorough examination in the anomalies as well as in the syndromes which are formed.

Returning to malformations of maternal dietary origin, it should be pointed out that vitamin B deficiencies other than that of riboflavin have been investigated, and some were found to be capable of inducing malformations. In some instances the missing dietary factor could not be established,

Fig. 6 A–C Sections through bones of young of mothers irradiated on the thirteenth day of pregnancy (250 r).

A. Humeroradial bone (× 16) showing firm osseous connection between humerus and radius.
B. Humeroradial bone (× 16) showing cartilaginous union of structures and lack of development of elbow joints.
C. Fibula has remained cartilaginous but beginning ossification is noticeable in the tibia. Since the proximal tibiofibular joint has not formed, the two bones appear fused.
D. Cleft palate in young after irradiation of mother on the fifteenth day of pregnancy. (Fig. 6 B, C, D from Warkany and Schraffenberger, '47.)

but it seems that the multiple malformations observed in pigs by Ross and coworkers ('44) and hydrocephaly encountered in rats by O'Dell *et al.* ('51) can be attributed to lack of factors of the vitamin B complex. Giroud and Boissot (Giroud, '52) observed congenital malformations of the eye and of the brain which they attributed to pantothenic acid deficiency.

Fig. 7 Sections of internal organs of young of female rats irradiated on the thirteenth day of gestation.

A. Abnormal brain (× 9) (300 r).
B. Abnormal brain protruding through skull (× 10) (300 r).
C. Median, fused kidney (× 13) (250 r).

Karnofsky and others ('49; Snell and Cravens, '50) induced congenital malformations in fowl by pteroylglutamic acid deficiency and Giroud and Lefebvres-Boisselot ('51; Giroud and Lefebvres, '51) by a similar deficiency obtained congenital abnormalities in rats. By incorporation of succinylsulfathiazole and a pteroylglutamic acid antagonist (x-methylpteroylglutamic acid) into a maternal diet lacking pteroylglutamic acid Nelson, Asling, and Evans ('50, '52) have recently produced multiple congenital abnormalities with regularity in the young of rats. Thus, by combination of a dietary deprivation with the feeding of an inhibitor and of an antagonist, an effective pteroylglutamic acid deficiency was produced. In this interesting investigation it was found that complete resorption of the embryos invariably occurred when rats were placed on the diet the day of breeding (Nelson and Evans, '47). If, however, the deficient diet was instituted on the tenth day of gestation,[3] 100% of the young born were deformed. When instituted on the eleventh, twelfth, and thirteenth days 95, 65, and 30% respectively were abnormal; when the mothers were submitted to the deficient diet as late as the fifteenth day none of the young were abnormal. The congenital abnormalities obtained in this way consisted of cleft palate, syndactylism, renal and pulmonary underdevelopment, and edema. Large supplements of pteroylglutamic acid to the deficiency diet permitted normal reproductive performance and prevented anomalies in the young. It seems that the teratogenic diet developed by Nelson, Asling, and Evans ('50, '52) when given from the tenth to the twenty-first day of gestation is the most effective teratogenic diet known at the present time.

Experiments with maternal dietary deficiency may be considered as a new tool of experimental embryology. In most studies of that science, eggs of fishes, amphibians, and birds have been used to produce morphologic changes by altering the chemical environment; advances in the science of nutri-

[3] These investigators designate the day of finding sperm in the vaginal smear as day zero and the following day as day 1 of gestation.

tion have made possible the study of mammalian ova under varying chemical conditions, and it seems that only a beginning has been made in this new field. In the experiments described no attempt was made to simulate human dietary conditions, and it is unlikely that human congenital malformations can often be attributed to maternal dietary deficiency. Only in populations which are restricted in their food supply by isolation, customs, or violence, can conditions arise which are comparable to the experiments cited. Endemic cretinism caused by maternal iodine deficiency is a case in point, but it remains to be seen whether there are other comparable conditions which can induce congenital anomalies.

Experiments of maternal dietary deficiency should have a permanent place in mammalian teratogenic research. In this connection it seems worth while to point out the relationship between malformations induced by maternal dietary deficiency and malformations of genetic origin. While these two kinds of malformations differ completely both in their origin and in their importance for the species, they do show points of similarity in their morphology and in their mechanism of development, which deserves to be emphasized.

By experiments with maternal dietary deficiency, types of congenital malformations can be induced which resemble, morphologically, malformations of genetic origin. Such imitations have been called phenocopies, a term coined by Goldschmidt ('38). Phenocopies are congenital nonhereditary malformations which duplicate malformations induced by mutant genes. For instance, cleft palate or syndactylism or coloboma of the retina may be of genetic origin; similar anomalies can be produced experimentally as nonhereditary phenocopies by riboflavin (Warkany *et al.*, '43b), pteroylglutamic acid (Nelson *et al.*, '50) or vitamin A deficiencies (Warkany and Schraffenberger, '46).

A second resemblance between effects of abnormal genes and effects of nutritional deficiencies is observed in the formation of syndromes of multiple anomalies. An abnormal gene frequently has a pleiotropic effect; it may cause malformations

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in a variety of organs which seem to be unrelated to each other in postnatal life. The Marfan syndrome and the Laurence-Moon-Biedl syndrome may be cited as examples from the field of human teratology and many similar syndromes have been described in rodents (Grüneberg, '47). Pleiotropic but nonhereditary effects have been observed as the result of experiments with maternal dietary deficiency. For instance, lack of vitamin A results in anomalies of the eye, of urogenital organs, and of the cardiovascular system. Nutrition experiments of this type result, therefore, not only in phenocopies of single organs but also in phenocopies of syndromes.

A third resemblance is that both a genic deficiency and a continuous nutritional deficiency act throughout the organogenetic period and that in both cases the embryo develops against a background which is permanently abnormal. In contrast are the acute teratogenic agents, such as the rubella virus or X rays, which attack the embryo but once and at a definite time. Genic and nutritional deficiencies are chronic abnormal states of prenatal life. They remain latent during some periods but become manifest in others when special demands are made by the embryo's metabolism (Landauer, '36).

Geneticists interested in teratology and in developmental genetics have long recognized the importance of the experimental production of phenocopies in the study of malformations of genetic origin. Dunn ('39–'40) has pointed out that the responses which a growing organism can make are directed into a limited number of channels and that environmental agencies may produce phenocopies by altering some developmental processes in the same way that gene changes or other mutations do. Landauer ('36, '40; Landauer and Bauman, '43) has used experimental induction of phenocopies to investigate the mechanisms by which the creeper mutation and rumplessness of fowl influence embryonic development. A knowledge of the abnormal channels opened up by modifying factors may throw some light on the mode of action of abnormal genes. Since little is known about the biochemical

reactions of genes which lead to malformations, a knowledge of the reactions which lead to their phenocopies may be of value. Phenocopies induced by nutritional deficiencies can be attributed to a lack of well-defined chemical substances. Purines and pyrimidines which are synthesized with the aid of pteroylglutamic acid (Nelson *et al.*, '50, '52) as well as riboflavin are incorporated in prosthetic groups of enzymes. Some of these enzymes participate in biochemical reactions which determine the channels of embryonic development. Experiments of the type cited in this review indicate where biochemical reactions necessary for normal development can be blocked. It is possible that mutant genes are inadequate because they are unable to control the same critical reactions. It seems to me that in this field the geneticist and the nutritionist are approaching common ground and it is to be hoped that they will unite their efforts in the near future.

This paper began by presenting the results of experiments but factual reporting seems to have slowly drifted into hypothetical interpretation. The interpretations are open to criticism and dispute, but this may lead to a fruitful discussion.

DISCUSSION

L. B. Russell: In connection with your comparison between the effects of X rays and of riboflavin deficiency, I am wondering whether the more widespread action of the X rays may not have been due to a high dose having been used? As we tried to show in our paper, increase in dose leads to an extension of responding period. Thus, in your experiment, irradiation with a high dose on the thirteenth day might be expected to yield not only the abnormalities most easily produced at that stage, but also others which, with a lower dose, would be elicited only by irradiation on the twelfth or fourteenth day. This idea finds support in the close resemblance of your radiation results for the thirteenth day to our summed results for days 10½ and 11½ (the mouse stages corresponding to your thirteenth and fourteenth days). It is therefore not impossible that, if you were to use a dose

low enough to elicit only those changes most characteristic of thirteenth-day treatment, you might get a closer correspondence with the riboflavin-deficiency data. On the other hand, of course there may be (as we showed in our paper) real differences between the basic actions of the two teratogens.

WARKANY: I think it would be very interesting to attempt to produce the same syndrome by X rays and by riboflavin deficiency, as suggested by Dr. Russell. Whether it can be done, I do not know.

HICKS: Dr. Warkany and Dr. Wilson, in their published studies, emphasize something that has been very useful to all workers on the mechanisms of malformations from the medical point of view. That is, it is useful to think of these malformations as products of two factors — the *time*, which we have been emphasizing here, and the *agent*.

In my paper I tried to show, for example, that in the developing nervous or skeletal system the same lesions cannot be produced with acute hypoglycemia as with radiation or "radiomimetic" drugs.

Dr. Warkany and Dr. Wilson have shown other examples with dietary deficiencies although the duration of action of these procedures is a factor to be considered.

FUJII: One wonders whether there is a relation between vitamin deficiencies and irradiation. It is possible that irradiated animals, in general, are unable to synthesize vitamins or that their vitamin requirements are higher. More specifically, embryonal cells which have been slightly damaged are unable to use vitamins essential for their vital synthesis. How to demonstrate this is the problem. With animals having placenta, obviously this could not be done with ease. If irradiated cells are unable to utilize the vitamins (not simply take them up), the blood and tissue vitamin levels would probably be altered. I wonder whether, in animals without placenta, vitamin utilization studies might not be valuable. The opossum might be a suitable animal for such studies, but more than likely one would have to go to lower species.

There may be some blood-brain barrier with respect to protective substances available to cells of the central nervous system, and this may include substances needed for cell synthesis.

Chairman WEISS: I think I should like to reemphasize the reversal of an antero-posterior gradient in the susceptibility of the skeleton, where apparently after riboflavin deficiency, the posterior border is hit first so much more frequently than the anterior border that the ossification center in the marginal cases is dislocated toward the anterior border; whereas after X-ray treatment, I think you got exactly the reverse.

This type of reversal makes it almost impossible to explain the effectiveness of any of these agents in terms of particular susceptible phase; it is a very important observation.

STUEHLER: When vitamin A deficiency was supplemented, the figures indicate that approximately 33% of the animals studied possessed abnormalities on the unsupplemented diet — of which 17% involved cardiovascular abnormalities. On the other hand, in the 13-day supplemented material, some 25% of the animals showed abnormalities of which 70% were cardiovascular. If you multiply these numbers together you find that there is actually an increase in the number of cardiovascular abnormalities on a thirteenth-day supplemented diet.

Might not some caution be used in ascribing any of these particular abnormalities to the direct effect of any particular growth factor on the formation of the structures studied? Could it not just as well be something very indirect, some influence on some secondary product of the mother?

In relation to this, I wonder whether there is a general correspondence between the abnormalities that you observed in embryonic development and the abnormalities which such riboflavin deficiency, in particular, produces in young adults, e.g., lack of proper ossification, etc.

WARKANY: We, too, have asked ourselves why there was an increase of cardiovascular anomalies when vitamin A was added on the thirteenth day. We think that some young with cardiovascular anomalies would have died in early intrauterine

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life without the supplement, and by giving the supplement, we saved some of them. This is one explanation, but we cannot prove it.

Whether riboflavin deficiency damages the embryo directly or whether the effect may be indirect and due to an injury to the mother remains an open question. I should not be surprised if a future need for reconsideration of the effects of riboflavin deficiency should arise. We consider these experiments as pilot experiments which require further study.

It should not be forgotten that our experiments were begun at a time when it was necessary to prove that congenital malformations of mammals could be produced by environmental factors. This was denied by many at that time, although it is generally accepted today. We have continued working along these lines but there is still much to be done. I think the reasons that more has not been done already is that nutritional teratogenic experiments are so tedious and disappointments are frequent.

WAELSCH: I should like to comment on Dr. Warkany's distinction between chronic and the more immediate effects. I wonder whether one is justified in considering the effect of rubella, for example, and of X rays as definitely of the immediate and nonchronic type? To my knowledge, nothing is known about the mechanism of the rubella effect on developing human embryos, and I think the preceding discussions at this conference have shown that really very little is known about the mechanism of the X-ray effect. So I could well imagine that these effects are as "chronic" as some of the other effects, e.g., genetic or nutritional effects.

To come back to the discussion of the relative incidence of cardiovascular abnormalities in general, when dealing with a syndrome of abnormalities, it is very difficult to establish the relative frequency of the individual symptoms if you look only at newborn animals. The relative frequency varies throughout the embryonic period because there is prenatal death, i.e., selective prenatal death of embryos, with certain abnormalities, which would, of course, influence considerably

the relative frequency of the individual symptoms of a syndrome.

GRUENWALD: I am glad to hear that the idea of the critical period being the only determining factor is losing ground. Particularly in the medical literature on rubella, there is considerable misuse of this concept when people claim that one thing happens during the second month, and another during the third month. The second month, after all, is not homogeneous. Human embryos at the beginning and at the end of the second month are quite different. I think it should be made clear that the specific influence of a given agent is in many instances more important than the exact time with which it acts, particularly because some of these agents apparently act for a long period of time.

Chairman WEISS: At the same time is it not a truism that if we choose to designate the period during which a tissue can be affected as the "critical" period, then that tissue can be affected only during the critical period? The question, therefore, is merely whether this "critical" period is the same for all agents, all stages, and all organs. Apparently, that is not the case, but there are still some critical periods.

GRUENWALD: We seem to come to the assumption, which is probably the only biologically correct one, that both factors act together: in some instances the critical period is more important and in some instances the agent is more important in determining just exactly what is going to happen. Would you agree to that?

Chairman WEISS: Not quite. I think the scientific procedure is simply to define what each partner in the process is doing. No biological system operates in a vacuum: it is always a cell reacting to something outside the cell. All we can do is simply describe this interaction. There is no point to the question as to which of the two is more important. If you take either one away, you get nothing.

SCHOTTÉ: I should like to attract attention to another phase of the problem of morphogenesis, the one which is encountered in regeneration. Students of regeneration, also,

have elaborated a series of devices by means of which teratological interferences on morphogenesis can be studied. It is amazing to discover that, in regeneration, interferences with morphogenesis can be obtained which constitute a corollary to that which has been so exhaustively discussed here. These interferences are multiple. First, there are purely physical factors such as various manners of amputations which subsequently impose upon the regenerate changes in morphogenesis. Then there are interferences with hormones (thyroid, parathyroid, pituitary). Recently we were able to show that a critical period in respect to the action of the pituitary on the morphogenesis of the blastema exists: if the limb of a newt is allowed to regenerate for 5–7 days and then the pituitary is removed it has been shown that the subsequent morphogenesis of the regenerate is affected, but only for that period. In others words, if a limb is amputated prior to the removal of the pituitary, then club foot formations, syndactyly, brachymely, and other teratological interferences with the morphogenesis of the blastema result. However, the fundamental processes of regeneration, including growth and histogenesis, are not affected by the hormonal imbalance created.

With respect to the action of the nervous system it has been shown that the susceptible "critical period" of interference with morphogenetic processes is a different one. Singer has shown that the emancipation of blastemata from nerve influence takes place between the eleventh and fifteenth days. Dr. Brunst has also shown many years ago (1928) that the nervous system plays an important role in the creation of skeletal abnormalities. The same fundamental processes of morphogenesis, then, reveal themselves to respond differently in respect to the agents employed to test these processes.

So it is indicated, I think, in a conference devoted to the study of the action of radiations on growth and development, to suggest that the pioneer work which Drs. Butler, Brunst, and others have done with respect to the action of X rays on regeneration of limbs in amphibia be extended and correlated with the findings on mammalian embryogenesis which were presented at this conference.

RUSSELL: I should like to reply to Dr. Waelsch's statement that one should not necessarily expect an acute effect from an agent which appears to have acute action, by pointing out that, on the other hand, one need not necessarily expect a chronic effect from an agent that appears chronic, such as a gene which is, after all, present from conception to birth. Actually, for many genes there are probably restricted periods for primary action which is called for by conditions arising in the course of differentiation.

In the general discussion on "critical periods," I should like to emphasize that this phrase is used by us merely to designate an end result, i.e., the developmental stages at which radiation has to be applied to produce a given change in character. The term certainly does not imply that the immediate primordium of the character malformed as a result of irradiation at a certain stage was damaged at that stage, i.e., during the critical period. The fact that different patterns of sensitivity may be demonstrated by the use of different teratogens is quite compatible with the concept of "critical periods" as used by us.

WARKANY: I should like to state here why some of us are so concerned about the indiscriminate use of the term "critical period." I think all of us in this conference understand how complicated the establishment of "critical periods" is and that the term is interpreted differently by different people.

We are concerned about the overemphasis and misinterpretation of the idea of "critical periods" as used at the present time in the medical literature. There you find statements which indicate not only that there are critical periods for the origin of certain malformations, but it is also asserted that one can ascertain from a malformation the time at which the injurious agent acted.

This is not just a point of theory. Let us assume that the symptoms of a clinical syndrome can be attributed to arrest of development of several structures in the eighth week of

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fetal life. Does that permit the conclusion that the arrest of development is due to environmental interference at the time when the fetus was eight weeks old? I doubt that anybody here will draw such a conclusion, but there are statements to that effect in the recent medical literature. Mongolism, esophageal atresia, and "retrolental fibroplasia" have been attributed to maternal disorders at a certain date of pregnancy, because the morphology of the anomalies can somehow be correlated with embryologic events at that date.

We have to make it clear that such conclusions cannot be drawn. It has been stated, for instance, that a persistent ostium primum in mongolism indicates that the septum primum and the endocardial cushions developed adequately until about the seventh week, when they were arrested just short of fusion. This is not correct, since the decisive arresting factor may have acted much earlier; yet the interference does not become recognizable before the eighth week. The best example in this respect is the open ductus which may result from maternal rubella in the first two months of pregnancy. The ductus fails to close at birth or after birth, but the injurious agent acted seven months earlier. The "critical period" is not the time when the ductus fails to close, but the time of a much earlier stage of development when an injury to the vascular system predetermines the persistence of the ductus. Although the anomaly does not "appear" until birth, the damage is done much earlier.

The morphology of congenital anomalies does not permit us to draw definite conclusions as to their date of origin. There are practical considerations involved. If the simplified idea of "critical periods" should reach the lay public we must expect serious consequences. If, for instance, a woman who had an automobile accident in a taxicab during the seventh week of pregnancy, gives birth to a mongol child, she could sue the taxi company. This will happen when we let this erroneous idea of critical periods become too widespread.

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HICKS: On the other hand, a malrotation of the gut of cyclopia or an encephalocele could not happen as a result of a birth injury.

WARKANY: I think the embryologic time table can be used to state that a malformation must have been caused *before* a certain time but one cannot say how early before the "critical period" the injurious agent acted; but even this may not always be possible since congenital malformations may be caused by secondary destructive processes after an organ had been normally formed.

WARLSCH: I should like to say just one word in response to Dr. Russell's remark. I do not think it is justified to call the effects of a gene, as you did, acute just because it has not been demonstrated to be "chronic," in quotation marks. You said one would expect to be able to demonstrate its effects in tissues other than the ones that are obviously affected. The failure to demonstrate it is not necessarily a proof that the effect is acute and not chronic. It may be just a problem of method and knowing what to look for in the effect of a gene.

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THE EXPERIMENTAL PRODUCTION OF CLEFT PALATE WITH CORTISONE AND OTHER HORMONES

F. CLARKE FRASER, H. KALTER, B. E. WALKER, AND T. D. FAINSTAT
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ONE FIGURE

Experimental mammalian teratology is rapidly establishing itself both as a method of embryological analysis and as a means of gaining understanding of the causes of congenital defects in humans. Hormonal aberrations (along with viruses, nutritional deficiencies, and hypoxia) might logically be suspected of being causally associated with "spontaneously" occurring congenital defects, since they are one of the hazards that a woman may actually face during pregnancy. It is therefore somewhat surprising that, until recently, hormones have received relatively little attention as teratogenic agents. The discovery in our laboratory that cortisone is teratogenic in mice (Fraser and Fainstat, '51) raises the question of whether this is so in man.

REVIEW OF LITERATURE

Before discussing our work on the teratogenic effects of cortisone the present paper will review briefly the studies of others on the embryonic effects of various hormones given to pregnant mammals.

Pituitary hormones. Due to the limited availability of pituitary hormones for research, little has been done on their teratogenic properties. Steiniger ('40) provided an interesting example of how an environmental agent can potentiate the effects of a genetic susceptibility. He showed that injection of

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tumor resulted in delayed weight gains when fed from the time of tumor implantation for the tumor-diet effects. Studies designed to characterize the unknown factors are now in progress.

CONGENITAL HYPERVITAMINOSIS A

A variety of congenital defects have been produced in rats by the administration of a single large dose of vitamin A on the ninth, tenth or eleventh day of pregnancy.

It has been reported that very high doses of vitamin A given the pregnant rat influence the development of the fetus (*Nutrition Reviews* **15**, *335* (*1957*)). The resultant abnormalities include anencephalia (absence of brain), anophthalmos (absence of the eyes) or large, open, protruding eyes, spina bifida (absence of vertebral arches in the spinal column), cleft palate, malformation of the extremities, labial fissures and cataracts. These changes occurred even though the increase in vitamin A per fetus was from 4.15 I.U. in the controls to 10.08 I.U. for those from treated mothers.

Also, deficiencies of vitamin A, riboflavin, folacin, pantothenic acid, vitamin D and vitamin E have been reported to cause various types of congenital deformities (*Nutrition Reviews* **2**, *297* (*1944*); **5**, *74*, *89* (*1947*); **11**, *121* (*1953*); **12**, *189*, *343* (*1954*); **13**, *289* (*1955*); **14**, *283* (*1956*); **15**, *9*, *44* (*1957*)).

Recently, a detailed study has been conducted with rats on the influence of a single dose of 75,000 to 150,000 I.U. of vitamin A on the ninth, tenth or eleventh days of pregnancy to determine the nature of the underlying histological changes in the fetus (F. M. Deuschle, J. F. Geiger and J. Warkany, *J. Dent. Res.* **38**, *149* (*1959*)). Eight typical specimens with large and protruding eyes were selected from the offspring and serially sectioned. The eyes, although large and lidless, were otherwise almost normal in structure, and the investigators concluded that probably a series of underlying skeletal anomalies caused them to protrude. The lower part of the nasal passage was wider and the upper part narrower in the abnormal rats than in the controls. Where the naso-turbinal and maxillo-turbinal processes approach each other, the nasal passage was almost occluded.

Moreover, these fetuses had a posterior cleft palate and an ankylosis due to a narrow bony ridge between the lateral part of the upper jaw and the lower jaw. There was also a well-developed cartilaginous mass between the upper jaw and lower jaw in an area where there is ordinarily no cartilage. Varying degrees of deficiency were noted in the development of the alveolar processes. In addition, as many as 11 of the 12 molars were missing in some of the specimens. In other cases, the remaining molars were hypoplastic.

Thus the syndrome precipitated in these fetuses by the single administration of a large dose of vitamin A during pregnancy resulted in developmental deficiencies, but only secondarily influenced the eyes because of their relationship to this area. Mesodermal and ectodermal structures were affected and it was presumed that the dental anomalies were caused by the anomalies of the underlying mesodermal tissues.

This hypervitaminosis syndrome could be readily differentiated from that of riboflavin deficiency. In the fetuses produced by riboflavin-deficient rats, only the incisor teeth were affected, with the lowers more

were reduced in length in riboflavin deficiency whereas the proximal portions of the jaws were shortened in hypervitaminosis A.

On the basis of present knowledge, no correlation can be drawn concerning pregnancy in women. However, the striking

same with which it was produced would suggest cautious use of large and repeated doses of vitamin A during pregnancy. This caution would seem to be especially pertinent in view of the relatively small difference in total vitamin A content between the carcasses of normal and treated fetuses.

FLUORIDE IN RICKETS

Although the total fluoride taken up in bones is reduced under conditions of rickets, the ratio of fluoride to total bone ash is increased.

Deposition of fluoride in rachitic animals has been reported in two studies both of which pertain to elevated levels of fluoride (J. A. Shults, *Iowa Agr. Exp. Sta. Am. Rep.*, p. 78 (1936); C. A. Kempf and V. E. Nelson, *Proc. Iowa Acad. Sci.* **48**, *199* (*1941*)). It has also been noted that 300 p.p.m. of fluoride reduces the severity of developing rickets by increasing bone density (K. Morgareidge and S. B. Finn, *J. Nutrition* **20**, *75* (*1940*)). In addition, the life span of rachitic rats has appeared to be increased when fluorides are made available (S. B. Finn and M. Kramer, *Proc. Soc. Exp. Biol. Med.* **45**, *843* (*1940*)).

A more critical evaluation of the deposition of fluoride has been carried out by I. Zipkin, R. C. Likins and F. J. McClure (*J. Nutrition* **67**, *59* (*1959*)). In addition to fluoride levels, information was obtained on the fat, ash, calcium and phosphorus contents of the femurs, lower jaws and teeth. The study was especially designed to permit the separation of the effects of rickets per se and inanition.

The experimental diet employed in this study was one which was adequate in calcium (0.44 per cent) and vitamins, but extremely limited in phosphorus (0.015 per cent). Fluoride was added as 2.8 p.p.m. The control diet was supplemented with disodium acid phosphate to provide adequate phosphorus and an adequate calcium to phosphorus ratio (0.437 per cent calcium, 0.330 per cent phosphorus and 3.0 p.p.m. fluoride). Sprague-Dawley rats were divided into three equal groups; group one received the rachitogenic diet and groups two and three received the rachitogenic diet supplemented with disodium acid phosphate. Group two was pair fed to group three and group three was fed ad libitum. The rats were x-rayed after three weeks and sacrificed at six weeks.

Although they received equal quantities of food, the pair-fed non-rachitic rats gained significantly more than their rachitic pair mates. Rats fed ad libitum and receiving the phosphorus-supplemented diet showed weight gains of 2.3 g. per day and a food utilization ratio of 0.27 g. weight gain per g. of diet.

Radiographs revealed that the rats receiving a low phosphorus diet had developed rickets whereas rats given the phosphorus-supplemented diet were normal. Femurs and lower jaws of the rachitic rats weighed much less than those of their normal litter mates, but only small weight differences were observed in the teeth.

The mean concentration of fat of the femurs was greatest in the rachitic, next greatest in the pair-fed rats and least in the ad-libitum fed normals. Fatty contents of the lower jaws followed this same relationship, but no significant differences were seen among the molars and incisors of the three groups. The ash content of the bones

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SCHOOL OF VETERINARY MEDICINE, MADINGLEY ROAD, CAMBRIDGE

4 JULY 1959

NUTRITION AND REPRODUCTION

Morning Session

Chairman: DR J. HAMMOND, C.B.E., F.R.S., *School of Agriculture, University of Cambridge*

[Maternal nutrition in relation to abnormal foetal development]

By J. W. MILLEN and D. H. M. WOOLLAM, *Anatomy Department, University of Cambridge*

During the first 9 months of his existence, man's life hangs almost literally by a thread—the thread which connects him to the mother who not only breathes and excretes for the foetus but also digests food and furnishes nutriment for the growth of the new individual.

In this period of intra-uterine development in which the individual changes from a single cell to a complex creature of 200 billion or more cells, he is exposed to the influence of two principal factors: heredity and environment. The first of these, the hereditary factor, is already determined at the fertilization of the ovum, and there is, as yet, no evidence that it can be altered by any form of treatment, and although selective breeding is extensively practised in animals, the human population, despite the wishes of eugenists, is strongly resistant to restrictions applied to its mating habits. The second factor, the environment, is, however, of almost equal importance in the development of the foetus.

The environment of the foetus is its mother, and the development of the foetus is strongly influenced by nutritional factors which themselves reflect with considerable exactitude the state of nutrition of the mother.

The processes of nutrition, the term being used in its widest sense, comprise the ingestion of foodstuffs (including vitamins and trace elements) and their digestion, absorption and utilization, and the inspiration of oxygen and the expiration of carbon dioxide. The state of nutrition can also be influenced by the effects produced by the invasion of pathological organisms or by alterations in the hormonal, nervous or psychic balance.

The two sources of information concerning the effects of dietary and metabolic errors during pregnancy are studies carried out on the human population and animal experiments. Although it is from animal experiments that the mass of evidence that dietary errors can result in the production of congenital malformations has been obtained, a certain amount of information has been brought to light on

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OF THE NUTRITION SOCIETY

ONE HUNDRED AND TWENTY-SIXTH SCIENTIFIC MEETING
SCHOOL OF VETERINARY MEDICINE, MADINGLEY ROAD, CAMBRIDGE

4 JULY 1959

NUTRITION AND REPRODUCTION

Morning Session

Chairman: DR J. HAMMOND, C.B.E., F.R.S., *School of Agriculture, University of Cambridge*

Maternal nutrition in relation to abnormal foetal development

By J. W. MILLEN and D. H. M. WOOLLAM, *Anatomy Department, University of Cambridge*

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The processes of nutrition, the term being used in its widest sense, comprise the ingestion of foodstuffs (including vitamins and trace elements) and their digestion, absorption and utilization, and the inspiration of oxygen and the expiration of carbon dioxide. The state of nutrition can also be influenced by the effects produced by the invasion of pathological organisms or by alterations in the hormonal, nervous or psychic balance.

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the effects of maternal nutrition in the production of deformities in man. This information is difficult to interpret because of the many variable factors that have to be taken into account. To give but one example: although the quantity and nature of the food consumed in the home of a pregnant woman may be nutritionally more than adequate, the woman herself may not be consuming a proportionate amount of this food, or may, having ingested it, fail to digest, absorb or utilize the food. To assess her nutritional state on the basis of the food available in the home may lead therefore to erroneous conclusions.

Nevertheless it is worth noting that a number of reports have appeared which support the view that a low level of intake of the basic foodstuffs during pregnancy, with presumably some degree of associated vitamin deficiency, is associated with an increased incidence of congenital malformations. The carefully documented studies on the incidence of anencephaly carried out by Coffey & Jessop (1958) in Dublin have shown a relationship between the occurrence of this malformation and a poor state of maternal nutrition. Again Anderson, Baird & Thomson (1958) concluded from their work that 'primigravidae living in poor social circumstances have a higher risk than any other group of pregnant women of foetal death due to malformations of the central nervous system'. On the other hand Record & McKeown (1949) found no association between the incidence of malformations of the foetal central nervous system and the housing of the mother, and Edwards (1958) studying the incidence of similar deformities in Scotland noted that although there was a higher incidence in the lower social class, there was no decline in the incidence with the onset of the present period of generally improved nutrition.

The bulk of our information has therefore of necessity come from animal experiments. Somewhat surprisingly, there are few reports of the effects of total starvation during pregnancy on the incidence of abnormal offspring in experimental animals. Runner & Miller (1956), however, produced congenital malformations in mice by starving the pregnant animals for 24 h during the 8th or 9th day of pregnancy.

Much of our present knowledge deals with the influence of vitamin deficiency or excess in the production of congenital malformations. In this regard most interest perhaps attaches to the role of vitamin A. The induction of a state of hypovitaminosis A during pregnancy has been shown to result in the production of a wide range of malformations in the pig, rabbit and rat. Among the malformations produced in this way are anomalies of the eyes ranging from anophthalmia to microphthalmia (Hale, 1935; Warkany & Schraffenberger, 1944), abnormalities of the urogenital system including horseshoe-kidney and failure of the testes to descend (Wilson & Warkany, 1948), diaphragmatic hernia (Anderson, 1949) and hydrocephaly (Millen, Woollam & Lamming, 1953; Rokkones, 1955).

It is of interest to note that vitamin A is, up to the present, the only vitamin of which an excess has been shown to have a teratogenic effect in pregnant animals. The first report of the effects of hypervitaminosis A during pregnancy appeared 6 years ago when Cohlan (1953) showed that malformed young were present in the litters of rats that had ingested large amounts of vitamin A during pregnancy. Among the abnormalities which he noted were hydrocephaly, exencephaly, spina bifida and

cleft palate. Cohlan's observations have since been amply confirmed by other workers, though hydrocephalus appears to be an infrequent finding (Giroud & Martinet, 1954; Millen & Woollam, 1957; Warkany, Kalter & Geiger, 1957; Woollam & Millen, 1957).

Deficiencies during pregnancy of vitamins other than vitamin A also result in the birth of malformed young. The most exhaustively studied deficiencies have been those of members of the vitamin B complex. Hypovitaminosis has been induced by a deficient diet either alone or in combination with a vitamin antagonist. By this method it has been shown that abnormal young can be produced by deficiency of riboflavin (Warkany & Nelson, 1940; Giroud & Boisselot, 1947; Grainger, O'Dell & Hogan, 1954), of pantothenic acid (Boisselot, 1948; Nelson, Wright, Baird & Evans, 1957) or of folic (pteroylglutamic) acid (Richardson & Hogan, 1946; Giroud & Lefebvres, 1951; Nelson, Wright, Asling & Evans, 1955). Experiments have indicated that a deficiency in any one of these substances results in abnormalities of the brain, including hydrocephaly and anencephaly, defects in the development of the eyes, cardiovascular and urogenital anomalies and skeletal defects including cleft palate.

Cheng & Thomas (1953) have been able to produce a similar range of malformations by the use of a vitamin E-deficient diet.

Derangements of normal metabolism may occur either through a natural or an experimentally induced hormonal deficiency or by the administration of hormones in excessive quantities during pregnancy. Gross hormonal disturbances during pregnancy in man probably result in abortion, but probably of more importance from the standpoint of malformations are disorders of less severe degree or of short duration, which may be overlooked.

Hoet, Braeseur & de Meyer (1955) have drawn attention to the relationship between a reduced glucose tolerance in pregnancy, not amounting to clinical diabetes, and the occurrence of congenital malformations in man. The need for caution in the administration of cortisone during early pregnancy is suggested by the report of cleft palate in a child whose mother had been treated with cortisone (Harris & Ross, 1956). The association between naturally occurring thyroid deficiency during gestation and cretinism is too well known to require further comment. Experimentally, Langman & van Faassen (1953) have shown that partial thyroidectomy carried out in female rats shortly before pregnancy will result in the birth of young with cleft palates and eye deformities.

It has been shown experimentally that administration of cortisone increases the incidence of cleft palate in a genetically susceptible strain of mice (Fraser & Fainstat, 1951), and cleft palate has also been produced in rabbits by the injection of cortisone during pregnancy (Fainstat, 1954). The injection of insulin into pregnant animals may also provoke the appearance of malformations in the young. Smithberg, Sanchez & Runner (1956) were able to produce exencephaly and skeletal deformities in mice by this method, and malformations have also been induced in rabbits (Chomette, 1955; Brinsmade, 1957).

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An interesting line of research has been opened up by the discovery that the incidence of congenital malformations produced experimentally by hypervitaminosis A can be influenced by the concurrent administration of hormones and antihormones.

It appears from experiments carried out by us that though the concurrent administration of some substances has an augmenting or synergic effect on the incidence of abnormal young produced by hypervitaminosis A, other substances exert a protective effect. In experiments in which cortisone was given in addition to vitamin A there was an increase from 7·8 to 36·6% in the number of young with deformities of the brain and skull (Millen & Woollam, 1957) and from 29·7 to 100% in the number with cleft palates (Woollam & Millen, 1957). Treatment with methylthiouracil in the drinking water resulted in an increase to 68·8% in the number with malformations of the head (Woollam & Millen, 1958). On the other hand, the concurrent administration of thyroxine in one group of experiments, prevented the deformities due to hypervitaminosis A (Millen & Woollam, 1959). In another series, vitamins of the B complex were given at the same time as vitamin A and the incidence of young with cleft palate fell from 31·4 to 1·4% (Millen & Woollam, 1958*a*). Protamine zinc insulin administered concurrently with vitamin A and cortisone appeared to protect the young against the augmenting effect of the cortisone. Instead of an increase in the number of young with brain deformities there was a reduction to 1·2% (Millen & Woollam, 1958*b*).

Many lines of thought are suggested by these experiments. Is the effect of a hypervitaminosis A to produce a relative deficiency of other vitamins by displacement? Cortisone and insulin have important relationships to carbohydrate metabolism. Could it be that the basic defect in teratogenesis is an error in the metabolism of carbohydrates that is insufficient to manifest itself clearly on clinical examination? Certainly the observations of Hoet *et al.* (1955) on the association between a prediabetic condition during pregnancy and the occurrence of foetal malformations would support such a possibility.

This review of the relationship between maternal nutrition and abnormal foetal development has of necessity been both brief and compressed. There are two points that seem worth making in summing up. The first is the need for further investigation, from the clinical standpoint, of maternal nutrition during pregnancy, with particular emphasis on the possible importance of minor degrees of vitamin deficiency in the first 3 months of pregnancy. The second is the value of the teratogenic experiment as a test-tube, as it were, in which the interaction of vitamins and hormones may be studied. The solution of many other pressing clinical problems may well come from the elucidation of the problem of congenital malformations, and from the direction of our attention to some extent away from three score years and ten and towards that period when, in the words of Sir Thomas Browne (1643), 'we live, move, have a being, and are subject to the actions of the elements and the malice of diseases in that other world, the truest microcosm, the womb of our mother'.

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Body stores in human pregnancy and lactation

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It is generally believed that, in man as well as in animals, metabolism during pregnancy is strongly anabolic, storage tending to exceed the amount attributable to the growth of the product of conception and the enlargement of the organs of reproduction. The surplus is usually interpreted as a reserve for lactation, in which the trend is believed to be katabolic. But the evidence for man is scanty, and the great variation of the gain in body-weight in human pregnancy suggests that there must be many exceptions.

Metabolism during pregnancy

There was originally some controversy about the extent to which foetal growth depends on the adequacy of the diet taken by the mother, but most authorities now

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agree that within a wide range of dietetic conditions the human foetus will grow normally, if necessary at the expense of the maternal tissues. Thus, the needs of the foetus place a limit on maternal storage if the diet is inadequate for both.

The average primipara gains about twice as much weight during pregnancy as can be accounted for by the growth of the product of conception and enlargement of the organs of reproduction. Table 1 gives mean values relating to Aberdeen primiparae who were allowed to eat to appetite during pregnancy. The mean net gain of maternal weight was 4·1 kg, of which less than 2 kg can be accounted for in the breasts and uterus. Little or nothing is known about the nature of the material stored and the sites of storage.

Table 1. *Mean distribution among different tissues of gain in weight in pregnancy of Aberdeen primiparae who were eating to appetite*

Foetus, placenta, amniotic fluid	5·0 kg	Lost at parturition
Increase of plasma and extravascular water	3·4 kg	Quickly lost after parturition
Increase of maternal stores, including increased weight of uterus and breasts	4·1 kg	Persists after parturition
Total gain	12·5 kg	

Averages of this kind may be altered as a result of clinical policy. Pre-eclampsia, an abnormality of late pregnancy characterized by hypertension and often by oedema and proteinuria, is usually accompanied by high gains in body-weight, which many obstetricians try to prevent. Dieckmann, Turner & Ruby (1945) went so far as to say that the total gain of weight during pregnancy should not exceed 7 or 8 kg, and on this standard it would be almost impossible for the mother to store nutrients in her non-reproductive tissues.

Averages also conceal a wide variation. Many pregnant women gain less than half or more than twice the average amount of weight. At present, we have very little idea of the physiological and clinical significance of such variations. High gains appear to connote excessive storage of water as well as of 'solid' tissue and are accompanied by an increased incidence of pre-eclampsia, whereas low gains are associated with reduced birth weights (Thomson & Billewicz, 1957; Thomson, 1959).

Serial measurements of body composition during pregnancy are difficult. Most is known about changes in body water and its 'compartments', but some of the techniques used in the past are now known to be misleading. Calculations that involve the use of constants relating to the non-pregnant state, for example the intracellular water content, are also likely to be misleading; there is no doubt that the *milieu intérieur*, far from being constant, undergoes necessary changes during pregnancy. Much less is known about changes in the 'solid' tissues during pregnancy. Many pregnant women say that they 'put on fat', especially around the hips. Skinfold measurements may help to confirm such statements, but at present there seems to be no satisfactory way of measuring the total body fat gained or lost.

Storage can be measured also in balance studies. We will consider nitrogen metabolism only. Murlin (1917) and Mellanby (1933) believed that the nitrogen

balance during the first half of pregnancy is negative. Though the absence of satisfactory evidence in man was admitted, they considered a negative balance to be physiological, and due to extensive proteolytic activity by the trophoblast. Vomiting in early pregnancy was interpreted as a sign rather than as a cause of katabolism. The scanty evidence now available indicates that in man retention of protein is usual in early as well as in late pregnancy. Harding (1925) wondered if this might be a uniquely human characteristic.

A positive nitrogen balance is undoubtedly usual during the second half of pregnancy. Macy & Hunscher (1934) estimated that there is an average total retention during pregnancy of more than 500 g nitrogen, of which about 370 g are stored in the maternal tissues as a reserve 'to prepare the maternal body for meeting the physiologic needs of lactation'.

Most of the balances cover short periods only, and may not be reliable. But three continuous balances from mid-pregnancy or earlier to parturition agree in showing net nitrogen storage, after allowing for losses at parturition, ranging from about 200 g to at least 446 g (Hoffstrom, 1910; Wilson, 1916; Hunscher, Hummell, Erickson & Macy, 1935). If figures such as these are representative, the nitrogen must be stored as protein without much associated water; otherwise they are almost impossible to reconcile with the accepted averages for weight gain during pregnancy. It may be that nitrogen-balance experiments tend to overestimate the extent of storage, as is suggested by some studies of animals where the results have been checked by carcass analysis (Nehring, 1957).

Metabolism during lactation

We have reviewed this subject in more detail elsewhere (Hytten & Thomson, 1960).

Nitrogen balances are strongly negative for a few days after parturition, when the uterus is involuting and the maternal organism is readjusting to the non-pregnant state. The relatively few balances that have been made after the immediate puerperal phase mostly indicate retention. The reverse idea, that the balance is characteristically negative during the period of mature milk flow, seems to rest almost entirely on analogy with animals, and on one woman studied during her fourth lactation by Hunscher *et al.* (1935). In two previous lactations, the nitrogen balance of the same woman seems to have been positive (Hunscher, Donelson, Nims, Kenyon & Macy, 1932–3).

We therefore doubt that nitrogen katabolism is characteristic of human lactation. The losses of protein in breast milk are relatively small, usually less than 10 g/day and, if the diet is reasonably adequate, reserves should not be necessary. On the other hand, the production of milk may require the expenditure of at least 1000 kcal/day, an amount which may not readily be supplied from the current diet. Thus, the provision during pregnancy of a reserve of energy in the maternal tissues appears to have practical value. The storage of energy mainly in the form of fat rather than of protein seems probable.

If body stores are used during lactation, the mother must lose weight. Very little information is available. The few studies of metabolism during lactation in which

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changes of body-weight are given show gains as well as losses. We have compared trends in the body-weights of thirty-seven Aberdeen primiparae who lactated for at least 10 weeks and thirty-five who lactated for not more than 3 weeks. A majority in both groups lost weight, but more in the breast-feeding group, in which the average loss was also greater. The women who lost most weight suffered most from tiredness, backache and other symptoms of impaired health.

There seems to be no correlation between the amount of weight gained during pregnancy and the yield and composition of breast milk. Apparently the production of milk, like foetal growth, can if necessary proceed more or less normally at the expense of the ordinary maternal tissues. The provision of special stores during pregnancy thus seems to be more important from the point of view of the lactating mother's health and well-being than from that of milk production.

Conclusions

Obviously, more research is needed. It is certain that the balance sheet of storage and loss varies greatly. We need measurements of the amounts of materials stored or lost, and analyses of the clinical significance of different patterns. Only in this way can we decide what is 'normal' and physiological, and what indicates inefficiency or abnormality.

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The influence of nutrition on female fertility in some of the large domestic animals

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Little reliable information concerning the influence of nutrition on the fertility of larger animals exists. There have been few well-planned experiments, but many expressions of opinion based on field observations. The views put forward are often conflicting and irreconcilable with the existing circumstances, which tends to throw suspicion on those who attach importance to the influence of nutrition on the fertility of large animals.

In this contribution I propose to deal with cows and to compare ewes and sows with them. Although little work has been undertaken in this field, it will be impossible to refer to it all.

Energy

Blaxter (1957) suggested that impaired breeding efficiency can be due to a lack of energy in the diet, but Hignett (1959) expressed the opinion that, within wide limits, shortage of carbohydrate and protein in the diet is self-limiting in its effect on the breeding performance of female cattle. If the energy available is low anoestrus is likely to result. When the plane of nutrition is higher, i.e. sufficient to permit ovarian activity but insufficient to maintain growth or lactation, a mating will most probably be successful. Cattle receiving a still more generous ration show increased growth or milk yield or both, but we believe it is this last group that is most sensitive to a deficiency or excess of certain mineral elements in the diet so that fertility may be impaired.

In observations over a period of 3 years Foote, Pope, Chapman & Casida (1959) showed that the plane of nutrition seemed to have a variable influence on the reproductive efficiency of ewe lambs. One year the 'flushing' of ewes appeared to increase the number of ova shed, whereas another year a higher plane of nutrition was associated with an increase in early foetal deaths.

With the sow and the gilt Kvasnitsky (1956), Saunders (1958) and Gossett & Sorensen (1959) produced evidence that a high plane of nutrition is likely to reduce reproductive efficiency, although the first author also incriminates inadequate feeding as a cause of porcine infertility.

Fibre

Saunders (1958) recorded that, in a group of twenty gilts, a sudden change from succulent food to dry fibrous grazing resulted in severe constipation and eighteen of the animals produced partly stillborn litters.

Vitamins

Of the fat-soluble vitamins, vitamins A and D are important for reproduction in the larger animals. On the other hand, vitamin E deficiency has no influence on fertility in female cattle (Gullickson, Palmer, Boyd, Nelson, Olson, Calverly & Boyer, 1949).

Vitamin A. Vitamin A deficiency definitely leads to infertility in female cattle. Depending on the degree of the deficiency and the time at which it occurs, the signs associated with the reproductive mechanism include anoestrus, frequent return to service, abortions and the birth of dead and weakly calves at full term (Hart & Guilbert, 1933; Axelsson, 1947). Avitaminosis A is not uncommon among heifers yarded during the winter and receiving a ration consisting almost entirely of sugar-beet pulp and oat straw. In ewes Guilbert, Miller & Hughes (1937) state that shortage of vitamin A interferes with the establishment of pregnancy and leads to

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the birth of weakly lambs. With gilts, according to Saunders (1958), vitamin A deficiency increases the incidence of stillborn piglets.

Vitamin D. Wallis (1938) has produced evidence which suggests that a deficiency of vitamin D can lead to a fall in the fertility of female cattle. This finding is supported by the observations of Hignett & Hignett (1953). They pointed out that if the phosphorus intake was rather low (less than 20 g P_2O_5 in excess of the 23 g for maintenance and 19 g/gal milk usually accepted) then a widening of the calcium:phosphorus ratio led to no depression of fertility of animals mated in October and November, when presumably the vitamin D status was high, but led to a marked fall in breeding performance of animals served the following February and March (Fig. 1). It is of

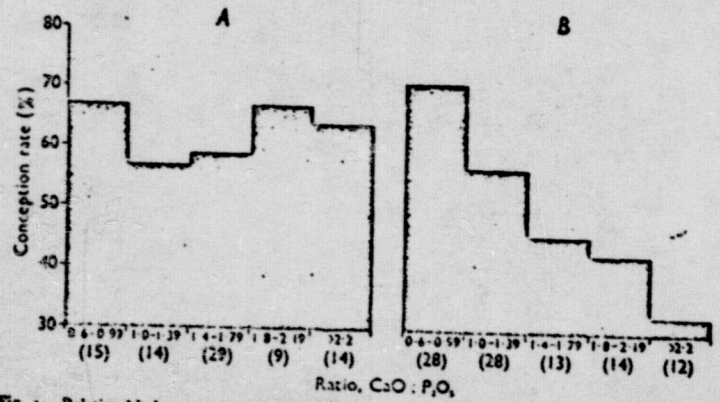

Fig. 1. Relationship between the ratio CaO:P_2O_5 in the diet and conception rate ((no. animals holding/no. mated) × 100) at first mating of cows receiving P_2O_5 less than 20 g in excess of the usually accepted amount of 23 g for maintenance and 19 g/gal milk and served during (*A*) October and November 1949 or (*B*) February and March 1950.
Significance of linear regression: (*A*) > 0·90; (*B*) < 0·02. Significance of deviations from linearity: (*A*) > 0·99; (*B*) 0·95. Figures in parentheses are the numbers of animals mated.

interest that these results were obtained during the winter of 1949–50, a winter following one of the best summers on record in the south of England. Present trends in crop husbandry and conservation—kale growing, silage making and grass drying—often result in carotene-rich feeding-stuffs being given to the almost complete exclusion of hay; and hay is the dairy cow's chief source of vitamin D during the winter months unless a vitamin D supplement is provided. Furthermore, it is accepted that some at least of these carotene-rich foods contain a factor antagonistic to vitamin D (Grant, 1951; Weits, 1952). Stockdale (1956, unpublished) obtained evidence that a low vitamin D status in pigs could have an adverse effect on reproductive efficiency.

Vitamin E. Although vitamin E is generally regarded as having little influence on the fertility of female domestic animals, Lunca, Bratescu, Otel, Maior & Siminel

(1956) reported that injections of this vitamin into sows on the 1st day of oestrus and again 15–16 days later led to an appreciable increase in litter size.

Water-soluble vitamins. As far as fertility is concerned the most important is probably vitamin B_{12}, a shortage of which occurs chiefly in ruminants suffering from cobalt deficiency. In affected females anoestrus is common, usually resulting from impaired appetite and greatly reduced food consumption. Dunlop (1948) claimed that the provision of cobalt supplements increased the lamb crop and decreased the number of barren ewes on the majority of Scottish hill gratings included in his investigations. There is also evidence that a vitamin B_{12} deficiency had an adverse effect on the breeding capacity of pigs (Mollgaard (1952), reporting the work of Moustgaard & Olsen).

Minerals

Of the minor mineral elements, cobalt has already been mentioned.

Copper. Absolute and conditioned deficiencies of copper are encountered in cattle and sheep in many parts of the world, including Britain. There has been some controversy about the effect of hypocuprosis on bovine fertility. In gross deficiency inanition occurs and anoestrus is not uncommon, but in less severely affected animals ovarian activity is maintained. It would appear that in the majority of herds with low blood-copper values there is impaired female fertility. On the other hand, there are some herds which have low blood-copper levels but maintain a high conception rate. These findings suggest that copper deficiency, absolute or conditioned, has little effect on breeding performance, but with hypocupraemic cattle of low fertility the administration of copper leads, almost always, to a sudden and dramatic improvement in fertility. With the ewe, low blood copper does not seem to reduce the size of the lamb crop. Nevertheless, because of the associated swayback, it may result in a marked reduction in the number of viable and useful lambs born.

Iodine. Iodine is usually considered an essential for normal reproduction of all species, but it is difficult to find conclusive evidence that iodine deficiency, absolute or conditioned, leads to infertility in cattle. Even when fertility problems are associated with thyroid dysfunction the latter is not necessarily synonymous with iodine deficiency. There is some circumstantial evidence that under certain conditions an iodine deficiency can interfere with the establishment of pregnancy in cows (Hignett, 1957). It has been suggested that goitrogens in kale and other members of the brassica family may lead to a conditioned iodine deficiency resulting in abortion or the birth of stillborn calves (White, 1954). With sheep it has been established that when pregnant ewes are folded on kale, the plant goitrogens present can lead to a very high percentage of weakly lambs, many of which die within 2–6 days of birth (Shand, 1952). The role of iodine in porcine reproduction is not clearly defined, but work in North America (Smith, 1917) indicates that iodine deficiency increases the incidence of stillborn and weakly piglets. According to the report very few young produced by sows on iodine-deficient diets survive for more than 36 h.

Manganese. There is much speculation about the importance of manganese in bovine reproduction. Hignett (1941) suggested that manganese deficiency leads to

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ovarian dysfunction in cattle. Bentley & Phillips (1951) produced more convincing evidence that adequate levels of manganese in the diet are essential for fertility of heifers. Seekles (1949) has also drawn attention to the importance of manganese. More recently, Hignett (1956, 1959) has produced evidence to support the view that the dietary level of manganese necessary for high female fertility depends on the relative amounts of certain major mineral elements and perhaps other nutritional factors present. Van Koetsfeld (1954, 1958) has shown that the manganese content of hair is related to conception rate. It is generally accepted that manganese is essential for breeding efficiency of sows and gilts.

Calcium and phosphorus. Of the major minerals, most attention has been paid to calcium and phosphorus. It has long been accepted that a gross deficiency of phosphorus, leading to clinical aphosphorosis, results in lowered breeding performance of cattle (Du Toit & Bisschop, 1929). In such animals there is a high incidence of anoestrus. Cows will come on heat after calving and, if served then, do not return to service, but on examination are found not to be in calf. Hignett & Hignett (1951) produced evidence suggesting that the recommended levels of dietary phosphorus for dairy cows, to which reference has already been made, were not always adequate for normal fertility of cows and heifers. Furthermore, with such levels of phosphorus, a widening of the calcium : phosphorus ratio of the food could depress fertility still further. As previously mentioned, planned feeding experiments demonstrated that the heifer's requirement for manganese for high fertility is largely determined by dietary calcium and phosphorus (Hignett, 1956, 1959). The dietary calcium : phosphorus status (x_1) was assessed by the use of the formula $\frac{P^2}{Ca}$ (where P is the oral consumption in g of elementary phosphorus for each 100 lb body-weight and Ca the corresponding measure of calcium). When manganese consumption was low (less than 40 mg elementary manganese/100 lb body-weight) fertility could be high when calcium and phosphorus were balanced (x_1 = 1·0–2·0). On the other hand, if dietary manganese levels were high (more than 100 mg/100 lb body-weight) fertility was high when calcium was excessive relative to phosphorus or vice versa (x_1 <0·5 or >3·75). This finding is well illustrated in Fig. 2. Further experimental evidence has shown that, even with a high consumption of manganese, it is possible to get calcium and phosphorus so very much out of balance that fertility of heifers is impaired. Analysis of feeding-stuffs used at the three Bull Progeny Testing Stations in the United Kingdom indicates that during a series of first matings of first-calf heifers at those centres, during the years 1955, 1956 and 1957, the dietary calcium, phosphorus and manganese levels placed all animals in the top right-hand corner, i.e. in areas *B*, *C*, *E* or *F*, of the field shown in Fig. 2, at the time of first mating. It is probable that, in the average herd, animals fall into this part of the field at the time of service. The whole story of the calcium–phosphorus–manganese complex and its influence on bovine fertility suggests that major minerals affect the utilization of the manganese required for one or more enzyme systems essential for the establishment and maintenance of pregnancy. In fact, one is left wondering if there is not an

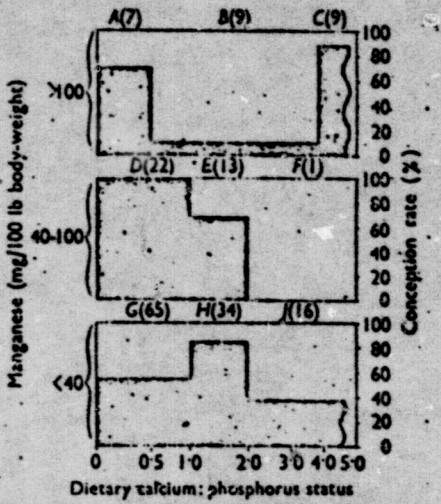

Fig. 2. Relationship between dietary calcium, phosphorus and manganese and conception rate (no. animals holding/no. mated) × 100) at first mating of heifers. The dietary calcium : phosphorus status, x_1, is determined by the formula $\frac{P^2}{Ca}$ where P is the intake of elementary phosphorus in g/100 lb body-weight and Ca is the intake of elementary calcium in g/100 lb body-weight. Figures in parentheses are the numbers of animals mated.

important connexion here with the most interesting and valuable observations of Lutwak-Mann and her colleagues on the biochemistry of the foetus and its immediate environment (Lutwak-Mann, 1955–6; Adams & Lutwak-Mann, 1955–6; Jacobson & Lutwak-Mann, 1956–7).

Oestrogens

Since Bennetts, Underwood & Shier (1946) demonstrated that oestrogens in subterranean clover could lead to reproductive disorders in sheep in Western Australia, much thought has been given to the possible effect of plant oestrogens on the fertility of grazing animals. The true position with regard to cattle has not yet been assessed, although Rowson (1959) has cast new light on the possible role of these oestrogens in bovine infertility. It may be that plant oestrogens and minerals have a joint effect. There is circumstantial evidence that these oestrogens can depress porcine fertility (Saunders, 1958).

Conclusions

In this review little attempt has been made to suggest the manner in which deficiencies or excesses of dietary constituents influence reproductive efficiency. Gross deficiencies depress ovulatory activity and often result in anoestrus. On the

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other hand, when ovulation continues it is not always clear whether there is a failure of fertilization or an increase in prenatal mortality. There is evidence that plant oestrogens interfere with fertilization of ewes (Sanger & Bell, 1959) and also affect the time taken for cattle and sheep ova to reach the uterus (Rowson, 1959). A high plane of nutrition sometimes appears to increase ovulation rate in sheep (Foote *et al.* 1959); it also increases ovulation rate in gilts (Haines, Warnick & Wallace, 1959). The latter workers, together with Gossett & Sorensen (1959) have demonstrated that on such a ration there is, in addition, an increase in the percentage of prenatal mortality. With avitaminosis A it is thought by some that changes in the endometrium can prevent implantation. Deficiency of the vitamin during the later stages of pregnancy results in foetal death.

Finally, the importance of stress associated with growth rate and lactation cannot be overemphasized. Time after time it has been noted that the animals which first show the effect of deficiencies or excesses of dietary constituents are those receiving an otherwise desirable and liberal ration and hence showing a high growth rate or milk yield or both. This feature of nutritional disturbance is frequently overlooked and much confusion thereby arises because animals on a quantitatively poor ration and consequently showing little growth rate or giving poor milk yields have a high level of fertility provided their energy consumption is sufficient to maintain ovarian activity.

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Effect of nutrition on androgenic activity and spermatogenesis in mammals

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To define the nutrient requirements essential to the male organism for its normal reproductive function is by no means a simple matter. It is a problem of many aspects because the processes involved are subject to fluctuations even within a single species, according to climate, environmental conditions, food habits, and the age of sexual maturation. A further complication arises from the effects of so-called 'nervous', 'stress' or 'conditioning' factors which can alter the normal requirements of an individual for a specific nutrient by influencing the absorption of food, storage and utilization of metabolites in the tissues, and their excretion to such an extent that the result is 'malnutrition' in spite of adequate food composition (Ershoff, 1948). It must also be kept in mind that failures of reproduction brought about by 'malnutrition' may be aggravated by congenital anatomical as well as genetic factors. However, by far the greatest difficulty encountered in the appraisal of reproductive disorders due to 'malnutrition' is to distinguish between primary effects due to the lack of a specific dietary component such as a vitamin, a trace element, or an essential amino acid, and secondary effects arising from diminished appetite, inadequate food intake and, finally, inanition, all of which are sequelae of deficient diets. This is one of the reasons why pair-feeding is such an essential and important prerequisite for all experimental investigations on the relationship between nutrition and reproduction.

The literature on the subject of nutritionally conditioned reproductive failures in the male is vast and abounds in observations on testicular atrophy, gynaecomastia, diminished libido and impotence, associated with such conditions as diabetes, hepatic cirrhosis, atrophic glossitis, gingivitis, seborrhea, keratosis of the eyelids and others; in this category belongs also the important study of Evans & Burr (1927) on degenerative and atrophic changes in the testes and male sterility, associated with deficiency of vitamins A and E. Together, these and similar studies represent an imposing total of valuable data which have been comprehensively reviewed from time to time, in particular by Biskind (1946), Hertz (1946), Samuels (1948), Russell (1948), Mason (1949), Ferrando (1953), Meites (1953), Roche (1957), and more recently by Lutwak-Mann (1958).

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Summary Discussion

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I. Introduction

In presenting a concluding paper to the Symposium in honor of Professor Karrer's great contributions to organic chemistry and biochemistry, I propose to attempt an appraisal of the present state of a few aspects of work on vitamin A and to add to it a commentary based in the main on the topics discussed at this symposium.

I first became interested in vitamin A in 1926 or 1927, and having watched the subject grow I am well able to appreciate our debt to Dr. T. Moore, whose treatise on vitamin A (1957) reduces to order the scattered and voluminous literature and shows that this one compound, placed in its

renalectomy brought about no great change. Similarly, adrenalectomy of rats on a stock diet did not appreciably change the liver concentration of liver vitamin A_1, ubiquinone, and ubichromenol (Phillips and Morton, 1959). Vitamin E-deficient rats showed no rise in liver ubiquinone; ubichromenol was not found (Morton and Phillips, 1959c).

Small amounts of ubiquinone and very small amounts of ubichromenol were found in the normal kidneys of various species (Lowe *et al.*, 1957). The best source of ubichromenol was normal human kidney (Mervyn and Morton, 1959).

The rise in ubiquinone in vitamin A-deficient rat liver is discussed by Wiss and Gloor (this volume).

The later rise in ubichromenol may mean an *in vivo* conversion of ubiquinone. Although under certain conditions ubiquinone can be converted to ubichromenol *in vitro*, it seems very unlikely that the compound is an artifact of isolation. The natural product is optically active.

V. The Deficiency Syndrome

1. Bone and Nerve Symptoms

Dr. Moore has presented at this Symposium a very clear analysis of this problem. In spite, however, of all the work that has been done on the symptoms of vitamin A deficiency—loss of weight, loss of appetite, xerophthalmia, night blindness, and so on—the situation remains in many ways blurred and imprecise.

Some years ago in connection with our work on ubiquinone, my colleagues and I had occasion to study the vitamin A-deficiency syndromes in rats and guinea pigs, in young chicks and older birds, and it was the differences rather than the similarities between species that impressed themselves on our minds (Heaton *et al.*, 1955, 1957; Lowe *et al.*, 1957a). The deficiency state may possibly be based on a biochemical "lesion" common to all the species, in the sense that some fundamental process is blocked, but it must be admitted that such a view rests more on a faith in uniformity than on evidence. The rats on a vitamin A-deficient diet behaved in the expected manner; there was a slackening of "growth" (i.e. weight increase) followed by a weight plateau with subsequent anorexia, loss of weight, and xerophthalmia, with numerous other late symptoms of epithelial metaplasia. The sequence of events (or their consequences) was very different for chicks. Nerve lesions were dominant and indeed death occurred in the young birds before loss of appetite or any sign of xerophthalmia. In the older birds neural dysfunction and retarded sexual development were prominent.

Aberle (1934), Mellanby (1926, 1931, 1934, 1941, 1944), L. A. Moore (1939), Rao (1936), and their colleagues found that in some species nerve degeneration, evidenced by muscular incoordination, stiffness, deafness,

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and blindness, could result from diets low in vitamin A given over a fairly long period of time. The histological evidence of neural degeneration was convincing, but the notion that xerophthalmia was secondary to a nerve lesion could not be sustained. Indeed, rats that survived for some little time after the onset of rapid weight loss and the appearance of acute xerophthalmia often developed paralysis before death. L. A. Moore *et al.* (1935), in a very able paper, showed that in calves blindness brought about by vitamin A deficiency was a result of atrophy of the optic nerve caused by pressure of bone. The bony canal had become too narrow.

Now it must be remembered that the early distinguishing of vitamin A and vitamin D rested upon ascribing to vitamin D the regulation of calcium-phosphorus metabolism. Moore found it surprising that vitamin A too played a direct part in bone physiology, and he was more ready to consider elevated intracranial pressure as a cause of the lesions. On the other hand, Mellanby (1938) had observed deafness in vitamin A-deficient dogs and had traced it to lesions in the 8th nerve associated with bony overgrowths. L. A. Moore and Mellanby were independently forced to the conclusion that vitamin A-deficiency was somehow associated with abnormalities in bone.

L. A. Moore and Sykes (1941) however, established a four- to sixfold increase in cerebrospinal fluid pressure as a characteristic of vitamin A deficiency. The "fits" seen in cockerels (Lowe *et al.*, 1957*a*) deprived of vitamin A resembled the convulsions and faintings described earlier. Mellanby (1941) also observed a rise in intracranial fluid pressure in vitamin A-deficient puppies.

Woollam and Millen (1955) found that the raised cerebrospinal fluid pressure in chicks was an early manifestation of vitamin A deficiency, which preceded overt neural disturbance. Similar results had been obtained by other workers on calf, sheep, and pig.

Mellanby (1944), in a famous Croonian lecture, eloquently stated the theory that vitamin A regulated osteoclastic action and vitamin D regulated osteoblastic action. The function of vitamin A was manifested in the "modeling" of the collagenous bone matrix. Wolbach and Bessey (1941) advanced an alternative theory and ascribed the nerve lesions to mechanical damage resulting from arrested bone growth with continued normal growth of nerve. Rats subjected to simple undernutrition failed to grow, but no compression of nerves was seen.

Rigdon (1952), however, was not convinced that bony overgrowths were fundamental and held that there was a primary nerve lesion caused by degeneration of cells in the spinal cord. Blakemore *et al.* (1957) accepted the fact of a lack of balance between the growth of bone and nerve, but in the bovine they found no evidence of bony pressure on the nerve. Instead they recorded the lengthening, twisting, and kinking of the optic nerve. Finally

the nerve broke at the point of kinking with capping of the divided ends, which were joined only by connective tissue. It appears that the actual breaking of the nerve may be delayed until "growth under normal nutritional conditions has imposed a further stress on the primary anatomical lesion." It seems clear that vitamin A deficiency does result in nerve lesions which may be primary and irreversible. The issues concerning bone are still somewhat uncertain.

2. *Hydrocephalus and Congenital Abnormalities*

The work of Millen *et al.* (1953, 1954) recorded that rabbits born from mothers kept on a vitamin A-deficient diet often exhibited hydrocephalus. Ossification was incomplete, and no bony overgrowths were seen. The expanding brain under increased cerebrospinal fluid pressure brought about bone distortion, which would here be quite a secondary phenomenon. The primary effect was thought to be excessive production of cerebrospinal fluid. This notion is itself a little difficult since the fluid is continually produced and is normally balanced by absorption. The fundamental lesion is still elusive. The effects of vitamin A-deficiency on pregnancy (Section VI) and embryonic development are very serious (Mason, 1935; Newton, 1938; Hale, 1933, 1935, 1937; Anderson, 1941, 1949; Warkany and Schraffenberger, 1944, 1946). Woollam and Millen (1956) include the production of diverse major congenital abnormalities in the heart, kidneys, genito-urinary tract, eyes, ears, palate, and at other sites in the body in many species, and anophthalmos can occur in pigs. Vitamin A deficiency makes its greatest impact at the particular stage in gestation when the supply to the fetus falls below some critical level and some crucial process fails to proceed normally for want of the appropriate biocatalyst. This crucial process, if it exists, must have a high degree of generality for growth processes. In our work on vitamin A deficiency in the domestic fowl (Lowe *et al.*, 1957), there was marked retardation of sexual development in males and none of the vitamin A-deficient pullets laid any eggs.

The over-all picture of the damage done by vitamin A deficiency inspires awe. Dr. Moore says in his book: "It seems reasonable to conclude that vitamin A deficiency can have *primary* effects on nerves, bones and epithelial tissues." One can agree that the attempt to sort our primary and secondary effects has not been wholly successful. It is equally necessary to say that not one of these effects has yet been related to the chemical structure of vitamin A in a scientifically serviceable manner.

VI. Vitamin A and Pregnancy

Lund and Kimble (1913) observed that in pregnant women plasma vitamin A was lower in the third trimester than in the second, but that it quickly

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rose within 48 hours of parturition. Bodansky *et al.* (1943) made similar observations and agreed that there was no corresponding fall in the carotenoids of plasma. The differences in vitamin A levels were not great; thus for 70 women pregnant for less than 6 months, the average was 105 I.U./100 ml., and for 62 women pregnant for more than 6 months the average was 91 I.U./100 ml. plasma. Again, 26 women given 10,000 I.U. of vitamin A per day showed on the average 123 I.U./100 ml. whereas 27 undosed pregnant "control" subjects had 93 I.U./100 ml. plasma on the average.

Sutton *et al.* (1945) studied 28 cows before and after parturition. Plasma vitamin A levels (averaged) fell from about 74 to 35 I.U./100 ml. during the 3 weeks preceding parturition, then remained low for a week post partum and afterward rose quickly. Plasma carotene similarly fell from over 600 μg./100 ml. to under 400, and then rose rather slowly.

Goodwin and Wilson (1951) confirmed the main findings but thought that the changes were part of a more far-reaching metabolic display at or near parturition. The temporary fall may well result in part from the accumulation of vitamin A in the colostrum which is being formed in the mammary glands. Cow colostra with 600–900 I.U./100 ml. of vitamin A and 200–500 μg. of carotenoids per 100 ml. are several times richer in both components than the later milk. This applies also to other species.

Thompson and McGillivray (1957) studied cattle and heifers in New Zealand, where pasture feeding ensures a high carotene intake round the year. In spite of this, plasma levels of vitamin A and carotenoids were found to decrease at or near to parturition. Vitamin A alcohol fell from 90 I.U. to 53.3 I.U./100 ml. just after parturition and then rose until after 11 days a level of 80 I.U./100 ml. had been regained. The carotene level rose to about 1350 μg./100 ml. just before parturition and then fell abruptly to about 900 μg./100 ml. and further to less than 750 μg./100 ml. on the third day. Thereafter the carotene levels rose again.

Vitamin A ester, almost 5 μg./100 ml. one or two days before parturition, fell to about 3 μg./100 ml. from one to three days after parturition. Thompson and McGillivray interpreted the evidence as supporting the suggestion "that the decrease in plasma components is related to the extra drain of colostrum synthesis, rather than to any hormonal changes associated with parturition."

Lübke and Finkbeiner (1958) studied the serum levels of carotene and vitamin A in human pregnancy, at parturition and puerperium. This is an important investigation on a firm statistical basis.

Figure 1 illustrates the results. The mean serum vitamin A for healthy nonpregnant women (193 ± 24 I.U./100 ml.) fell abruptly (to 143 ± 28.3 I.U./100 ml.) at the onset of pregnancy and then slowly rose (to 166 ± 27.5) just before parturition. There was then a further sharp fall (to 125.3

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± 32.3 I.U./100 ml.). The level in cord blood was only about half that in maternal circulation. During the first few days after parturition the serum level rose considerably (to over 220 I.U./100 ml.) and thereafter fell to nearly the average figure for nonpregnant women. The figure also shows how the β-carotene level of serum also fell strikingly in the early period

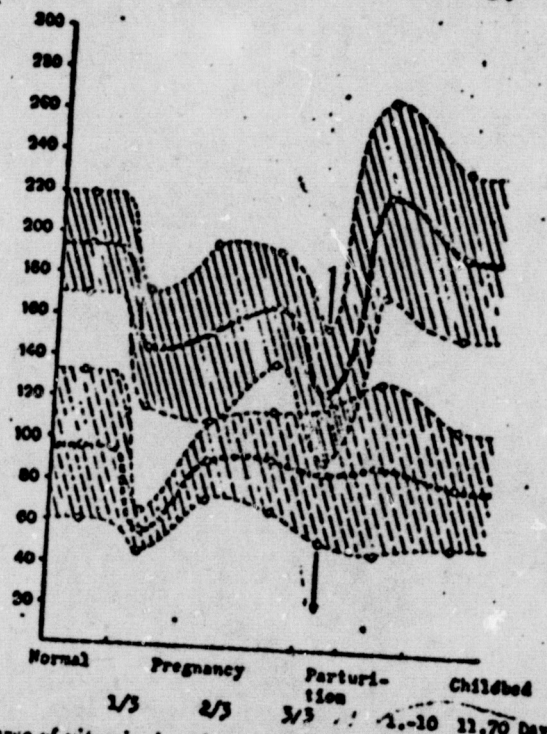

FIG. 1. Course of vitamin A and β-carotene levels in serum during pregnancy and in parturition and childbed, with corresponding standard deviations. Upper curve: vitamin A, I.U. per 100 ml.; lower curve: β-carotene, micrograms per 100 ml. After Lübke and Finkbeiner (1958).

of pregnancy but rose again during the second half to regain the initial level. The striking fall in vitamin A at parturition was not paralleled. The carotene level in cord blood was about 25% of that characteristic of maternal blood.

In a proportion of their cases, Lübke and Finkbeiner observed the presence in serum of unusual substances (possibly breakdown products of carotenoids) that interfered with spectroscopic assays. They were seen only during pregnancy and at parturition or during the first weeks post partum. These substances, about which little more was said, deserve further study.

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The fetus is well protected against excess of vitamin A or carotenoid. Only a small proportion of either finds its way across the placental barrier, and heavy dosing has but little effect. Liver reserves of the newborn are quite low in most of the species that have been studied. *Per contra* the colostra, rich in vitamin A and often rich in carotene, are well absorbed and so help to build up a store in the liver of the offspring.

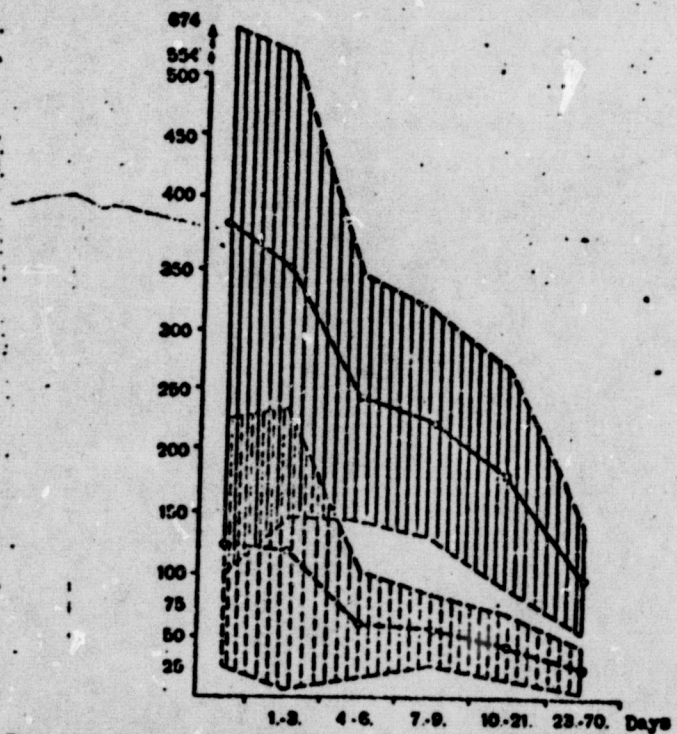


FIG. 2. Colostrum and milk: decrease of vitamin A and β-carotene values in mothers' milk. Upper curve: vitamin A, I.U. per 100 ml.; lower curve: β-carotene, micrograms per 100 ml.

It is quite clear, however, that the vitamin A and carotene levels of milk soon fall [Fig. 2, after Lübke and Finkbeiner (1958)]. Lübke and Finkbeiner (1958) write: "Schwerwiegende Folgen aus einer unzureichenden Versorgung mit Vitamin A im intrauterinen Leben und auch im Säuglingsalter sind bekannt. Die Seltenheit des Auftretens von manifesten Vitamin A—Mangelerscheinungen darf jedoch nicht dazu verleiten, die Bedeutung des Vitamin A zu unterschätzen." They recall a suggestion by O. Neumann (1950) that vitamin A acts as a catalyst for the transformation of cholesterol into progesterone. The implication here is that at the onset of pregnancy

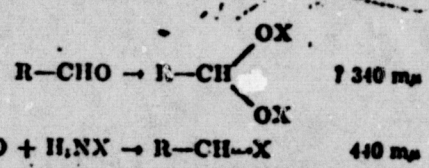
there is a sharply increased demand for vitamin A at some site or sites in the body and the rate of withdrawal of the vitamin from the blood stream temporarily exceeds the rate of mobilization of vitamin A from the liver reserve. There is no evidence that in these women the blood levels of vitamin A became dangerously low or that their liver reserves were depleted.

It is, however, important to consider what might have happened if the reserves had been low initially. There is also the rather uncomfortable feeling that magnitude of the normal liver reserves may sometimes lead to an illusory sense of security if they are not readily mobilized in physiological emergencies.

VII. Visual Pigments

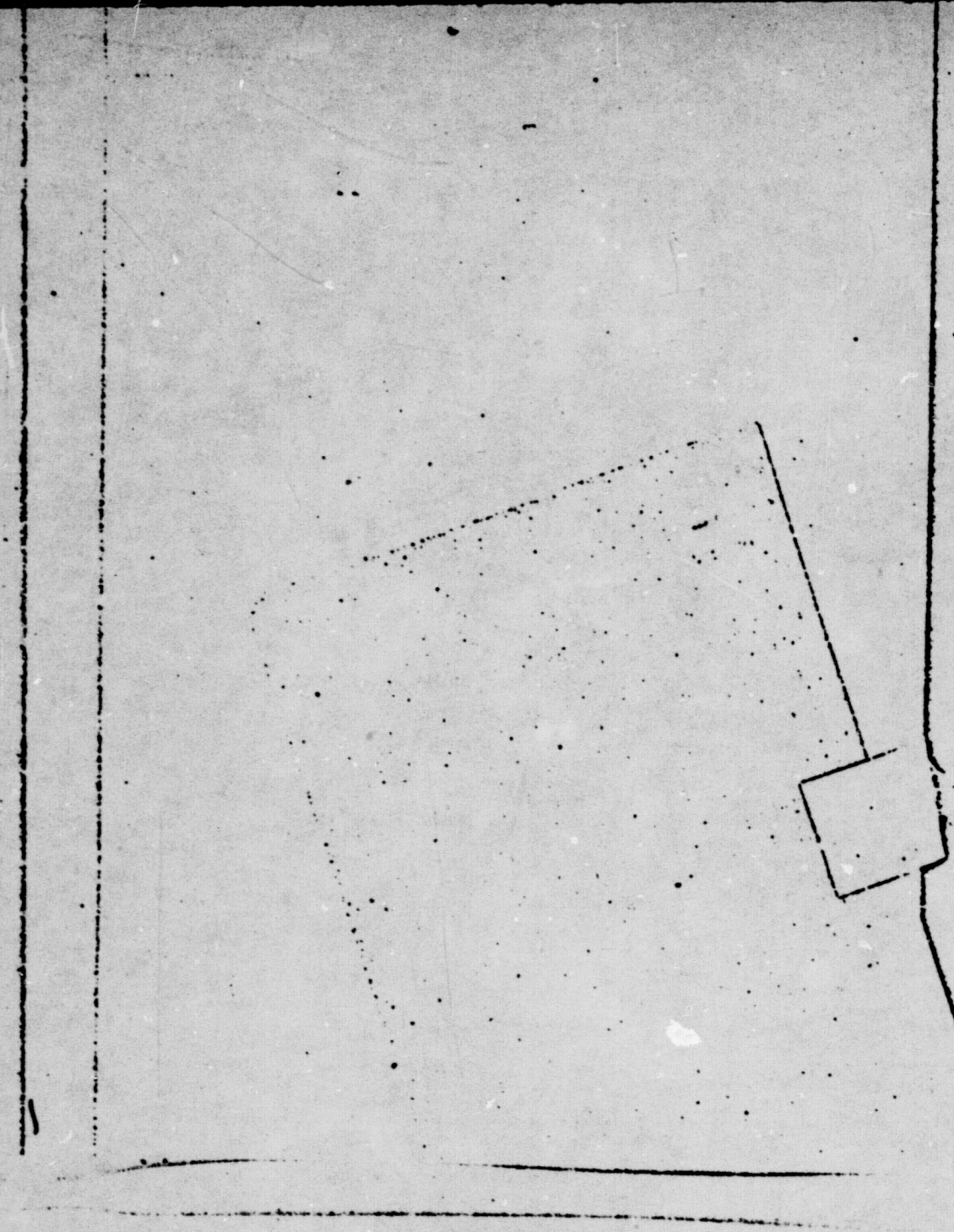
At this stage I have little to add to the recent brilliant work of Wald and his school on the role of *cis trans* isomerism (Wald, 1952, 1958). The elucidation of the relationship between one *cis* isomer and opsin to form rhodopsin leaves at least two major questions unanswered. First, there is no satisfactory explanation in terms of chromophoric groups of the plurality of visual pigments, nor for the shifts: rhodopsin (500 mμ) → porphyropsin (522 mμ); iodopsin (560 mμ) → cyanopsin (620 mμ).

The attractive work of Goldsmith (1958) on the visual system of the bee (*Apis mellifera*) by the recognition of retinene in the head tissue suggests that insect vision may have much in common with that of other animals. Yet the photosensitive substance has λ_{max} 440 mμ and is readily soluble in plain water. Further light-sensitive materials have sensitivity maxima at 335–340 and 490 mμ. To get from retinene$_1$ with λ_{max} 370 mμ to a substance with λ_{max} 335–340 mμ, it is necessary to neutralize the C=O chromophoric effect without producing the bathochromic shift seen in a Schiff base, e.g.



1. Action of Enzymes on Rhodopsin

Radding and Wald (1958) showed that chymotrypsin attacks rhodopsin in two stages: (1) an initial rapid process exposing 30 amino groups per molecule without bleaching and (2) a slower hydrolysis exposing about 50 additional amino groups *with proportionate bleaching*. Chymotrypsin attacks peptide linkages of aromatic amino acids with methionine, apparently in rhodopsin itself rather than in protein impurities. This seems to indicate fragmentation of rhodopsin without attack on the site of attachment of



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THE TERATOGENIC EFFECTS OF HYPERVITAMINOSIS A UPON THE FACE AND MOUTH OF INBRED MICE*

Harold Kalter

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Introduction

The field of experimental mammalian teratology has caught the interest of individuals in a large number of disparate biological and medical disciplines, such as anatomy, pathology, genetics, radiology, embryology, pediatrics, gynecology, zoology, dentistry, preventive medicine, epidemiology, psychology, plastic surgery, pharmacology, nutrition, cardiology, endocrinology, and biochemistry. Workers in each discipline seek answers to their own questions, of course, but each will surely discover that much can be learned from the research carried out in other disciplines.

Studies in experimental mammalian teratology have become very numerous (Kalter and Warkany, 1959*a*), and the number of known teratogens is relatively large. It is likely, despite contrary opinion, that each teratogen or class of teratogens has characteristic repercussions on embryonic transformation and growth; hence the continuing search for new teratogens is a legitimate one, aiming at discovering means of interfering with the development of specific organs or systems of the embryo that hitherto have not been disturbed teratogenically, and studying the resulting disturbances to learn about modes of normal and of "spontaneous" abnormal development.

There exists a wealth of studies on gene-induced dental anomalies, especially those in mice (Grüneberg, 1952); however, few experimental studies have been made of prenatal environmental influences on teeth. These were recently summarized (Kalter and Warkany, 1959*a*; Kreshover, 1959). Cleft palate and cleft lip, however, are rather common effects of teratogenic procedures, and these induced malformations have been studied intensively from various points of view (Warkany *et al.*, 1943; Kalter, 1954 and 1957; Nelson *et al.*, 1955; Walker and Fraser, 1957; Fraser *et al.*, 1957).

The teratogenic method employed in the study to be discussed is maternal overdosage with vitamin A. This method was discovered by Cohlan (1953 and 1954), and its effectiveness has since been confirmed several times (for example, Giroud and Martinet, 1955; Deuschle *et al.*, 1959). In our laboratory this technique has recently been applied to inbred strains of mice and has been found to produce in them severe congenital malformation of many parts of the body (Kalter, 1959; Kalter and Warkany, 1959*b*).

Among these malformations was a syndrome of anomalies of the face and mouth that is of especial interest because it contains features not previously described in the literature dealing with teratogenic studies.

Materials and Methods

Young adult female mice of the A/Jax, DBA/1Jax, and C3H/Jax inbred strains were placed with males of their own strains, one pair to a cage, and

observed each morning thereafter for a copulation plug. The presence of a plug was taken to indicate that ½ day had passed since conception. The impregnated female was then placed in a cage by herself and, at 8½ or 9½ days* after conception, was given one administration of 10,000 I.U. of vitamin A by mouth by means of a blunt-ended 19-gauge needle and tuberculin syringe. The vitamin, originally containing 300,000 I.U. vitamin A palmitate/cc. in sesame oil,† was diluted with sesame oil to 50,000 I.U./cc., and 0.2 cc. was administered. The animals were fed Purina Lab Chow and fresh tap water ad libitum throughout pregnancy. They were sacrificed 17½ days after conception, that is, approximately 2 days before term; resorption sites were counted and the fetuses were removed, examined macroscopically, and then fixed in Bouin's solution for serial sectioning or in 95 per cent alcohol in preparation for staining of the skeleton by the alizarin technique.

Results

To the time of writing no strain differences in type or frequency of induced congenital malformations have been detected; therefore the treated females and their offspring will be discussed without distinction as to strain. The effects of the vitamin on embryonic development were widespread (Kalter, 1959; Kalter and Warkany, 1959*b*). This report, however, deals only with malformations of the face and mouth, which were most severe and varied after treatment at 8½ and 9½ days after conception.

In 9 of the 23 females treated at 8½ days after conception, all (a total of 60 conceptuses were resorbed. The other 14 females produced 55 young and had 52 resorbed implantation sites. Eighteen females were treated at 9½ days after conception. In 1 female only was the entire litter (8 conceptuses) resorbed. The other 17 females had 97 young and 34 resorbed implantation sites.

On external examination the 152 young possessed the following congenital malformations of the face and mouth, exclusive of those of eyes and ears (the number in parentheses being the per cent showing the defect). At or near the corners of the mouth there occurred dermal tabs and hillocks of varying length and size (62.5 per cent). In many of the animals without such dermal appendages there occurred microstomia, that is, reduction in size of the oral aperture, ranging from a moderate decrease to apparent obliteration of the oral opening (33.6 per cent). Accompanying microstomia and seeming to parallel it in severity was a variable reduction in size of the proximal end of the mandible. In addition to this mandibular defect, there occurred micrognathia, that is, shortening of the mandible distally, giving a retrognathic appearance (17.8 per cent). Shortening of the upper jaw appeared in a few animals (11.2 per cent). In this study median cleft mandible occurred rarely (2.0 per cent), but in subsequent series it has appeared more frequently (see FIGURE 1 for illustrations of above-discussed anomalies).

Ninety-three of the animals' mouths could be opened and the palate examined; 52 of these had cleft palate. The remaining 59 had microstomia, which prevented examination of the palate without damaging the mouth, or were too fragile for this examination. Six of the 59 had unilateral or bilateral cleft lip

* Females were also treated at 7½, 10½, 11½, or 12½ days after conception, but the results of these

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occurs spontaneously in about 5 per cent of the young). Of the 53 without cleft lip, 16 were cleared for skeletal examination and 15 were found with cleft palate; 3 were serially sectioned and all were seen to have cleft palate. Therefore, of the total of 112 whose palates were examined in various ways, 70 cleft palate (62.5 per cent). This, of course, is an underestimate, since of the palates of the microstomic animals were not examined; in these anim it was discovered, the palates are most likely to be cleft, since 18 of 19 cle and sectioned microstomic specimens had this defect.

With the exception of cleft palate, these malformations occurred with roug the same frequency as a result of treatment at 8⅓ days after conception after treatment at 9⅓ days after conception. For dermal tabs these quencies of occurrence were 54.5 and 67.0 per cent, for microstomia 36.4 32.0 per cent, for micrognathia 18.2 and 17.5 per cent, and for cleft palate and 53.2 per cent, all respectively. The more frequent occurrence of cl palate after the earlier treatment in pregnancy therefore must have been d

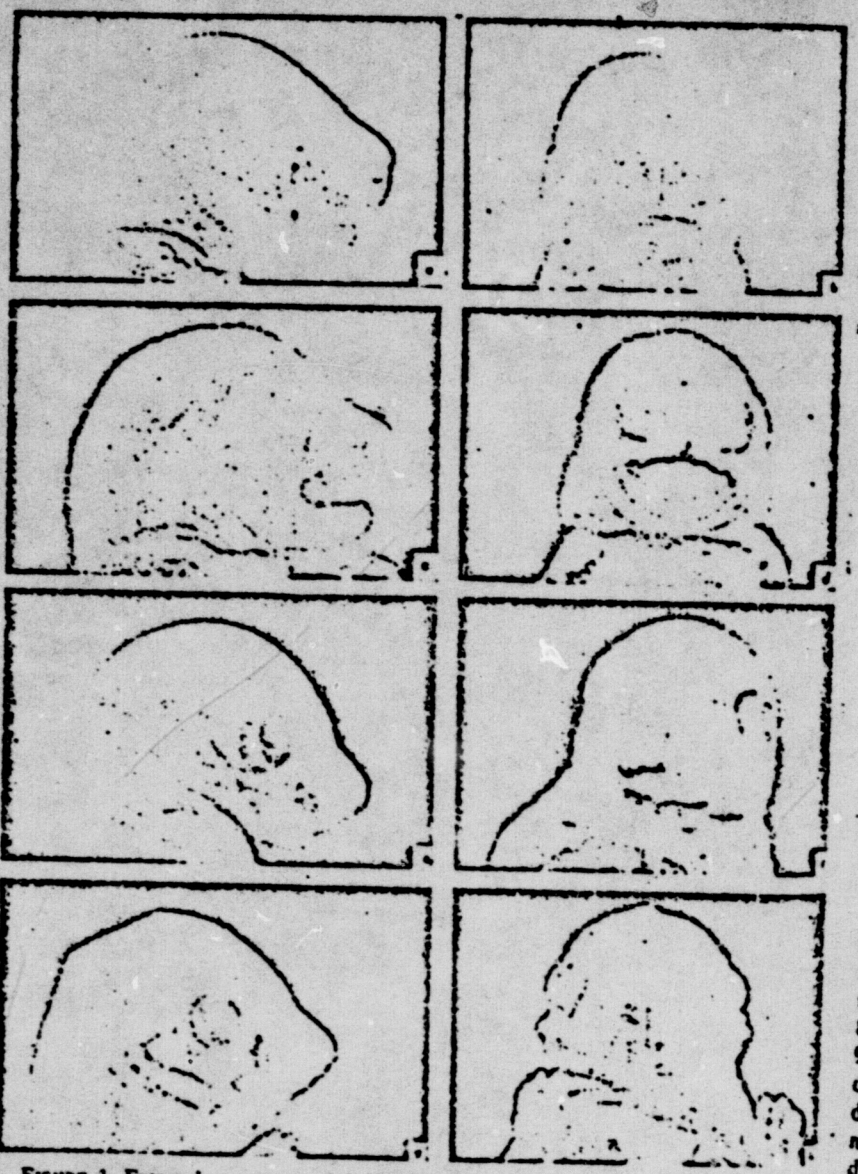

FIGURE 1. External appearance of the head. (*a* and *b*) Control; (*c* and *d*) experimental animal; dermal tabs; (*e* through *h*) different grades of microstomia and mandibular ma development.

FIGURE 2. Frontal sections through the level of the upper incisors. (*a*) Control; (*b*) experimental animal, showing minute mouth, thick oral epithelium, and short lower jaw.

to the fact that a greater proportion of nonmicrostomic animals were affected at that time than at the later time of treatment.

FIGURES 2 through 7 consist of comparable frontal sections from front to back through the heads of a control animal and an experimental animal from a female treated at 9⅓ days after conception; FIGURES 8, 9, and 11 are frontal sections through the head of an experimental animal from a female treated at 9⅓ days after conception. In such serially sectioned material, obtained from 9 animals treated at 8⅓ or 9⅓ days after conception, a remarkable array of defects was seen. The oral opening, as already mentioned, was variably reduced in size. Underlying this outward condition were extremely complex malformations of the mouth and its surroundings. The mouth itself was often drastically reduced in size (FIGURES 2 and 3), sometimes to such an extent that the tongue was tightly encased and distorted (FIGURE 4). One of the ... of this was a reduction ...

the recesses had been zippered up, leaving the abnormally thick oral epithelium projecting deeply into the tissue at the sides of the mouth (FIGURE 3). In addition, the oral cavity was diminished by the presence of the unascended and abnormally shaped palatine shelves, which fused in complex and varied ways with buccal surfaces of the mouth, leaving intricate and tangled oral pockets in the fused regions (FIGURES 4 and 5). Further back, the lateral and dorsolateral edges of the tongue became fused to gingival and palatine tissue, again leaving oral outpouchings between the lateral edges of the tongue and inner surfaces of the gums (FIGURE 6). As these outpouchings rapidly became occluded, all that was left of the mouth was a narrow, horizontal, crescent-

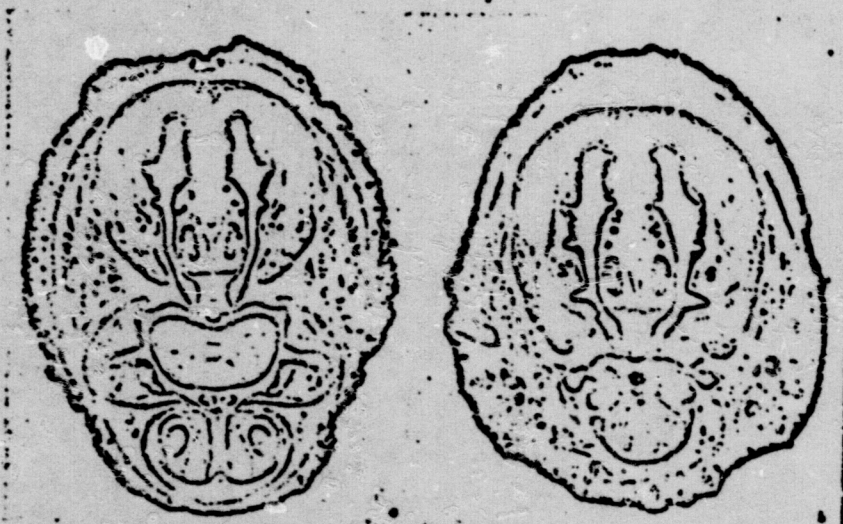

FIGURE 3. Frontal sections through the level of the internal nares. (a) Control; (b) experimental animal, showing small mouth, heterotopic cartilage, invaginated oral epithelium and short mandible, and ventrally enlarged rostral portion of maxilla.

shaped space, identifiable as the nasopharynx, between the dorsal surface of the tongue and the basocranium (FIGURE 7).

Various anomalies were found in the dental structures themselves, for example, fused, supernumerary, absent, and ectopic teeth. Lower incisors were generally normal except for occasional enlargement or slight inward rotation. In an instance of fused upper incisors, it was found that the lateral borders of the "tooth" were so situated as to indicate that the incisors proper were more or less normally located; however, it was as though an intercalated wedge of dental tissue had become fused to them. The entire mass consisted therefore, of a block of tooth much larger than the bulk of two incisors alone. A second incisive abnormality consisted of unilateral or bilateral supernumerary upper incisors. These were located posterior and lateroventral to the normally

At the fetal stage observed, the first lower molars in control animals the bell stage, the enamel organ is beginning the formation of the cusps and the connection between the enamel organ and the dental lamina is lost. Minute second molars are present. In general, anomalies of first consisted of their being absent, ectopic, misshapen, or smaller or larger normal. Ectopia of the lower molars consisted in their being located tissue causing the obliteration of the lateral recesses of the oral cavity. molars were turned on their side with the cusp pattern vertical and mediad and with the dental lamina horizontal and joined to the oral epi

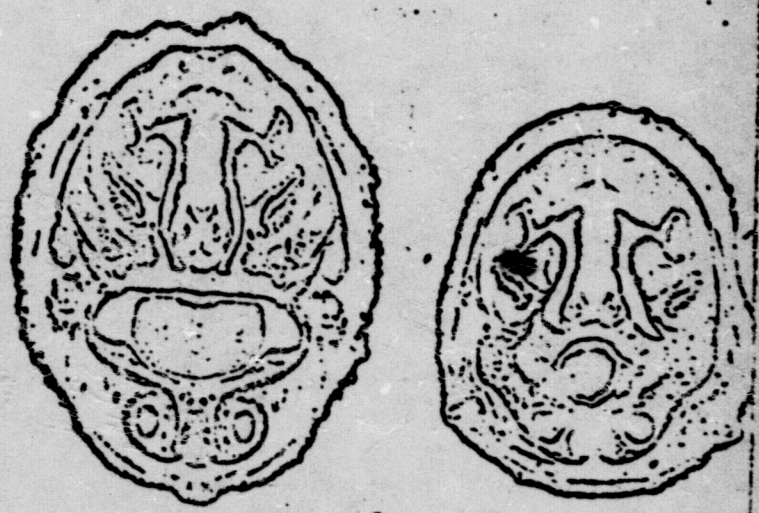

FIGURE 4. Frontal sections through preorbital region. (a) Control; (b) experimental animal, showing massive bilateral maxillomandibular ankylosis, small infraorbital fo small mouth and small, compressed tongue, abnormal course of the common nasal displaced nasal cartilage, absence of masseteric musculature, absence of sublingual da larged lower incisors, and other abnormalities.

at the lateral edge of the oral cavity. Ectopic upper molars lay far lat their normal position, in a bizarre location in the cheek. In this case the lamina took an erratic course, but failed to connect with the mouth (FIGU

Ectopia of molars was invariably associated with the trapping, by pie heterotopic cartilage, or oral epithelium that was invaginated into buccal This will be more fully described below.

The second molars were either apparently normal, absent or, in the c upper second molars, slightly shifted laterally. The last anomaly was pro entirely referable to the displacement of the gums caused by cleft pa ate. upper first molars were also slightly shifted.

Various skeletal elements of the face were often markedly abnormal. following description refers to

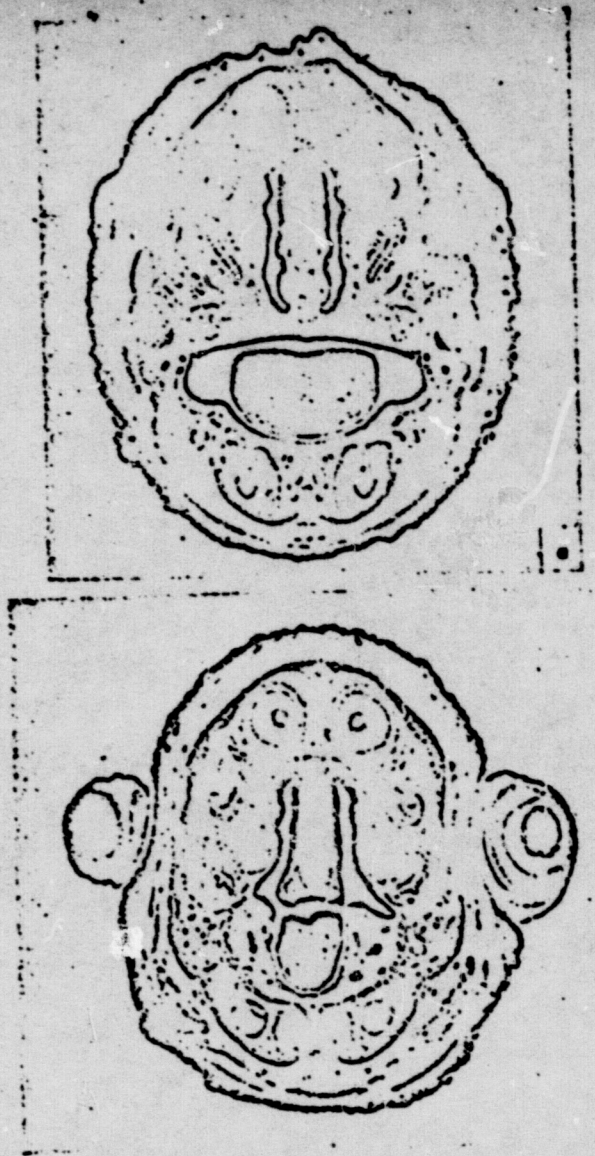

FIGURE 5. Frontal sections through the level of the anterior orbit. (a) Control; (b) ex perimental animal, showing much the same variety of anomalies as in FIGURE 43 and a cleft palate, unascended palatine shelves fused to buccal tissues with cross sections of on outpouchings in the regions of fusion, absence of parotid ducts, and heterotopic cartilage in th area of fusion of maxilla and mandible. Contrast of the abnormal animal with its matchi control shows also that the portion of the maxilla from which the zygomatic process norma originates is absent, with consequent absence of portions of skeletal elements of the orbit.

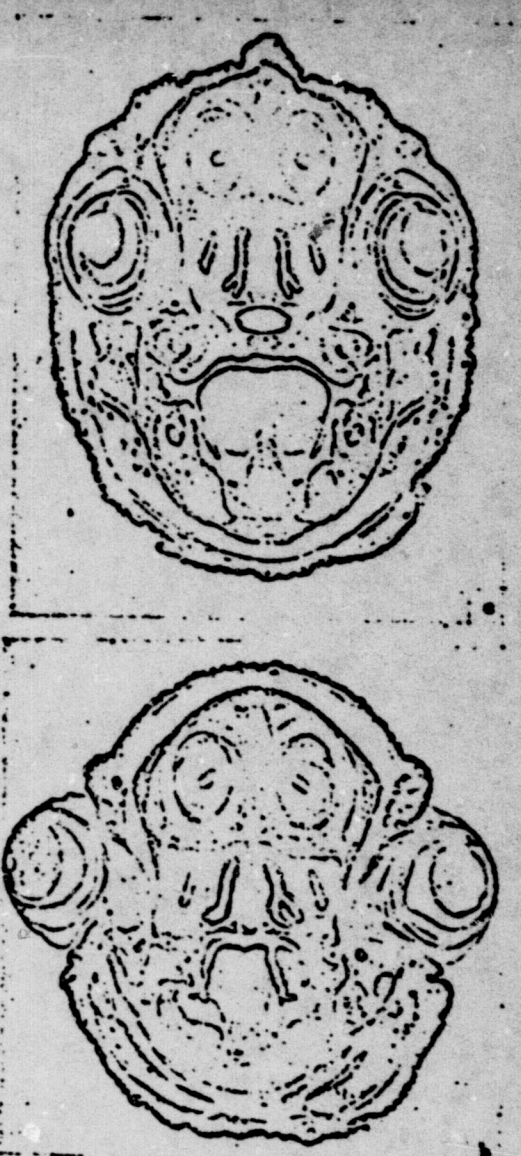

FIGURE 6. Frontal sections through the level of the first molars. (a) Contr perimental animal, showing absence of the first molars, the zygomatic process exte the region of maxillomandibular ankylosis (instead of from the crista facialis, as 5a), heterotopic cartilage large on the right and smaller on the left lateral to the or and beginning fusion of the tongue and gum on the right side. In this, as in sev sections of abnormal specimens, exophthalmia is present, being the product of much of the skeletal supporting structure of the orbit. Disorganized sublingual m is also seen.

cleared specimens (FIGURE 10) and as was confirmed in sectioned material (FIGURES 3 through 7), the mandibular ramus and its processes were entirely or nearly entirely absent, the mandibular body aberrant, and the maxilla and its various processes grossly deformed. At the level of the internal nares, the rostral portion of the maxilla was seen to be situated too far laterally and enlarged and extended ventrally (FIGURE 3). This ventral enlargement creased rapidly, only slightly more posteriorly, extending ventromedia form a thick and solid ankylosis with the dorsolateral margin of the mandi body (FIGURE 4). The infraorbital foramen was very small. The ventrola arc of nasal cartilage was displaced laterally, and the base of the common meatus projected far ventrolaterally instead of gently curving ventromed

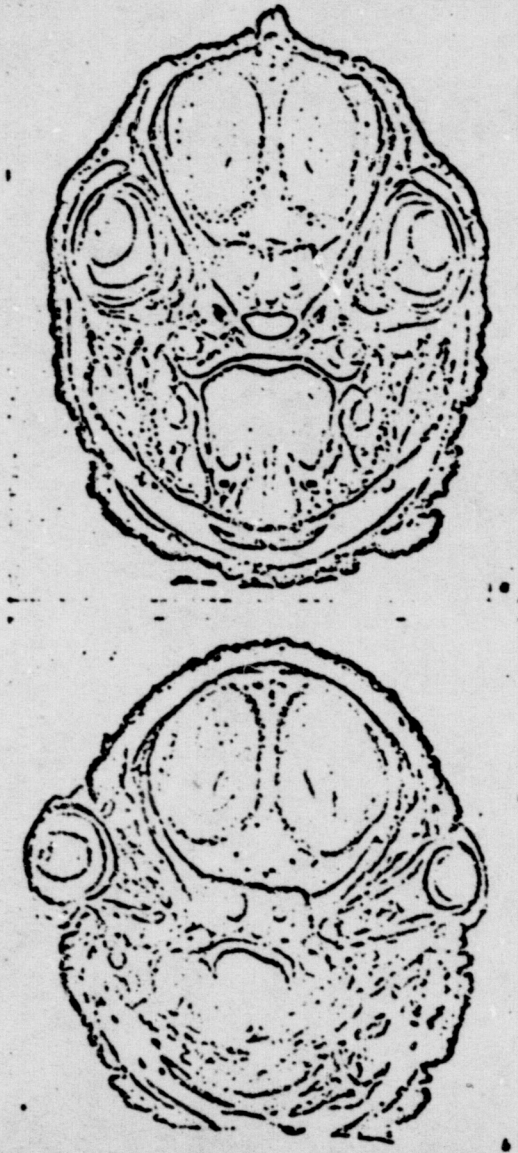

FIGURE 7. Frontal sections through the level of the optic nerve. (a) Control; (b) experimental animal, showing almost complete absence of the mandibular ramus, heterotopic cartilage at the corners of the oral cavity, the tongue immobilized by fusion to gums, cleft palate

FIGURE 8. Frontal section of abnormal animal showing supernumerary upper in bordered by heterotopic cartilage ventrolaterally and by an abnormal spur of maxilla late Compare with same section of control in FIGURE 3a.

(FIGURE 4). Further posteriorly, the zygomatic process of the maxilla, w was larger than normal, originated far too ventrally from the area of ma ankylosis of maxilla and mandible (FIGURE 5). The crista facialis of the ma was absent, with the consequence that, instead of arching gracefully out back, the zygomatic process emerged and coursed straight back, far too med (FIGURE 6).

Proceeding posteriorly, the mandible gradually diminished and nearly di peared, until only isolated osseous remnants around and close to the ma were left. With the almost total disappearance of the mandible, Meck cartilage

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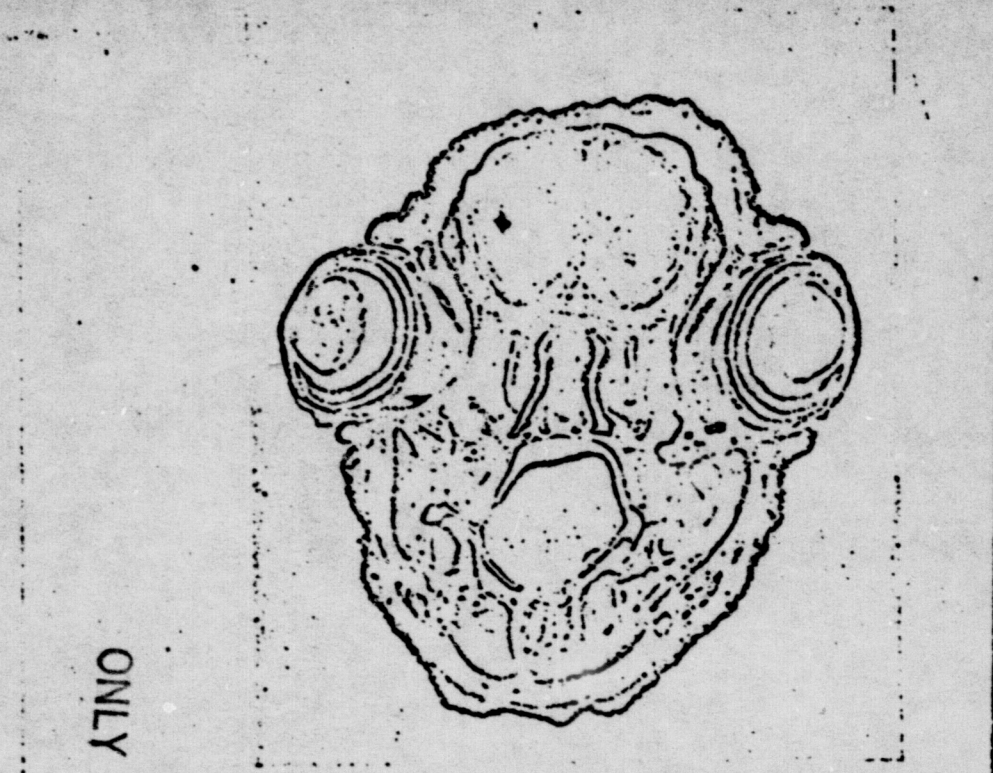

FIGURE 9. Frontal section of abnormal animal showing such effects as absent, ectopic, and abnormal molars. Compare with same section of control in FIGURE 6a.

variable-sized pieces of cartilage were present in areas surrounding the s generally in or close to bone. Heterotopic cartilage appeared at the c of the mouth near the lips (FIGURE 3), rapidly enlarging and, further, fusing with heterotopic cartilage present in the zygomatic bone, to form horizontal bars or other shapes of cartilage (FIGURE 11). Often the heter cartilage engulfed the fingers of oral epithelium that projected laterally the corners of the mouth, to form islands of this tissue. Proceeding poste

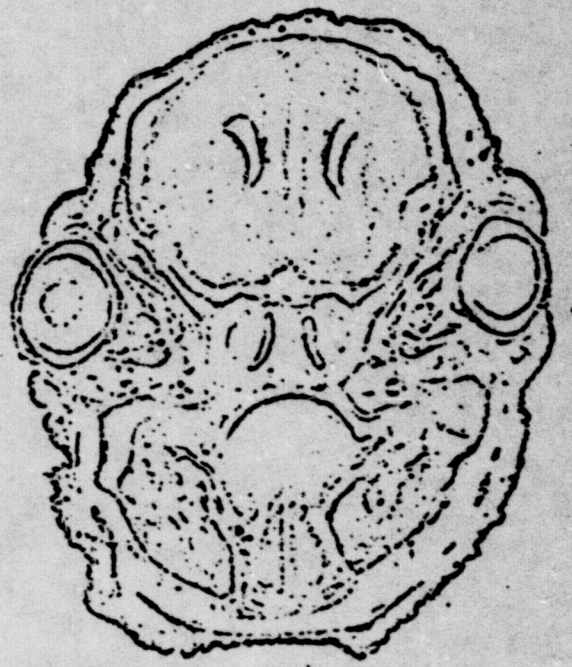

FIGURE 11. Frontal section of abnormal animal, showing fusion between hetero cartilage in zygomatic bone and that at corners of mouth. Note also the bridge betwee tongue and gum on the right and the dental anomalies.

the zygomatic bone became greatly thickened as it joined the zygomatic pro of the squamosal bone, investing and otherwise closely associating with ma of heterotopic cartilage as it did this.

Defects of various other soft tissues were also noted, among them disorgan tion and absence of sublingual and submaxillary muscles, absence of all p of the masseter muscle, absence of the parotid ducts and of the sublin glands and ducts, and unilateral absence of the submaxillary glands.

(1959), also using rats, found that "more proximal portions of the jaw" were affected. Furthermore, Giroud and Martinet (1958), using rabbits, reported a "complex case of microstomia," but apparently failed to affect the mouths of mice (Giroud and Martinet, 1959). Deuschle *et al.* (1959), however, produced a syndrome of dentofacial anomalies in rats greatly similar to the one described in the present paper for mice.

The animals described in this paper possessed a pattern of anomalies that presents certain features not often encountered in past teratogenic studies. Most induced anomalies of the face have consisted of fissures between various processes or decrease in size or absence of certain structures. In this study, on the other hand, were regularly found excesses of tissues, such as skin, bone, cartilage, and tooth.

It is probable that certain facets of this syndrome of dentofacial malformations were more immediate effects of the treatment and that others were more remote consequences of the earlier responses. To say which defects preceded and which followed, however, is not too easy in most cases, and a precise analysis must await pathogenetic investigations. It is not likely, however, that the dental defects were early results of the teratogenic agent; more probably they were mediated through and dependent upon anomalies induced in precursor and influencing tissues, such as ectoderm and mesoderm and, later, bone.

Studies such as this one, in fact, emphasize the interrelatedness and coordination of developmental events by showing how their deflection at crucial moments can reroute subsequent pathways and have unforseeable and far-reaching consequences. Such studies, therefore, can be valuable in the elucidation of normal patterns of sequences of embryonic events.

Summary

This paper describes and discusses the congenital malformations of the face and mouth in the offspring of inbred female mice given a large dose of vitamin A about halfway through pregnancy.

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Teratogenically Induced Congenital Aphakia*

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Forty-five offspring of pregnant DBA mice treated with a single large dose of vitamin A were serially sectioned. Nearly all of the young had bilateral "typical" retinal colobomas with otherwise well-developed eyes. One of them, however, had more severe abnormalities, consisting of a microphthalmic left eye and an extensively malformed right one, in which all of the structures of the anterior segment were missing. It was postulated that the aphakia and accompanying ocular anomalies were the consequences of total retinal coloboma, i.e., an exaggeration of the defect that occurred commonly, and that secondary destruction of the lens was responsible for its absence.

1. Introduction

Experimental mammalian teratology is concerned with the prenatal induction of congenital malformations in laboratory animals. The methods that have been used to produce structural deviations in embryos are numerous, and the types of abnormalities produced are many and diverse (Kalter and Warkany, 1959). These defects often closely resemble their human counterparts.

Among the most effective teratogenic (i.e. malformation-producing) means is hypervitaminosis A. Single large doses of vitamin A given to pregnant mice during early embryogenesis cause morphological anomalies of the face, mouth, heart, spinal cord, genitourinary system, rectum, skeleton, etc. (Kalter and Warkany, 1961). Recently, one offspring with an unusual malformation of an eye was found.

2. Methods

The mother of this animal, a mouse of the DBA/IJ inbred strain, was given a single dose of 40,000 IU of vitamin A palmitate in sesame oil by oral intubation. The administration was made at about 8-1/3 days after fertilization, i.e. early during the organogenetic period of embryonic development, at a time before the appearance of any optic structures. The pregnant female was killed about 2 days before expected delivery and the offspring removed, fixed in Bouin's solution, and serially sectioned at 20 μ and stained with hematoxylin and eosin.

3. Results and Discussion

The female had only one full-grown offspring. As Plate 1 shows, the offspring's left eye was microphthalmic. Its most distinctive features, aside from smallness, were the thick cornea and the absence of the anterior chamber and of the optic nerve (see the control eye in Plate 2). Plate 3 shows a frontal section through the brain at

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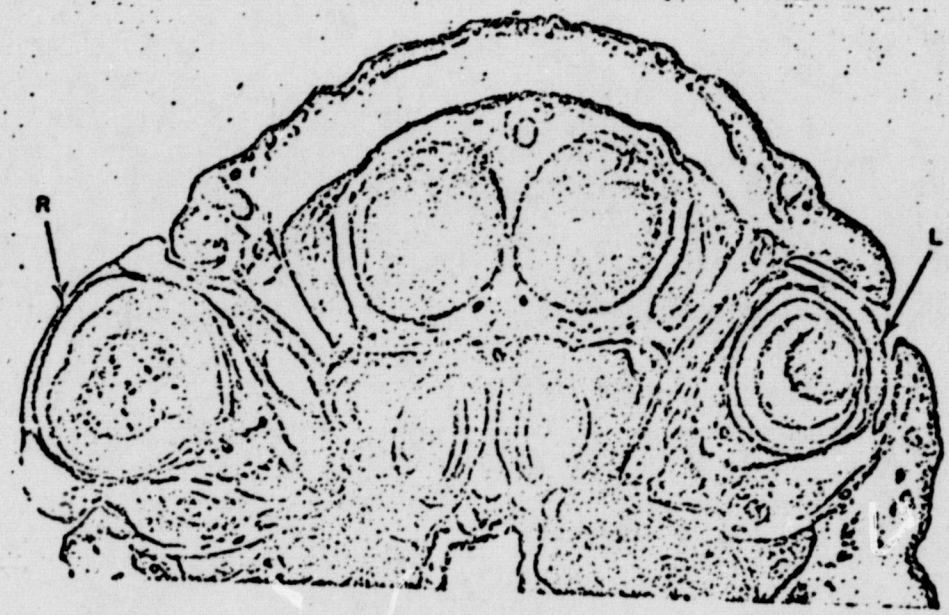
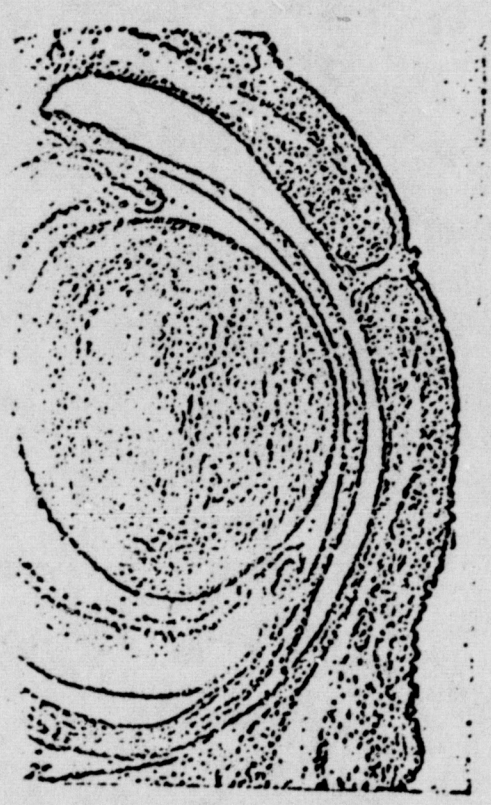


PLATE 1. Frontal section of head of late fetal mouse, in orbital region, showing animal's left eye (L) to be microphthalmic and right eye (R) to have abnormalities described in text. (Approximately × 30)



as that of abnormal specimen. Note closed eyelid, normal for
among well-developed, relatively large lens, well-contoured
ately × 75)

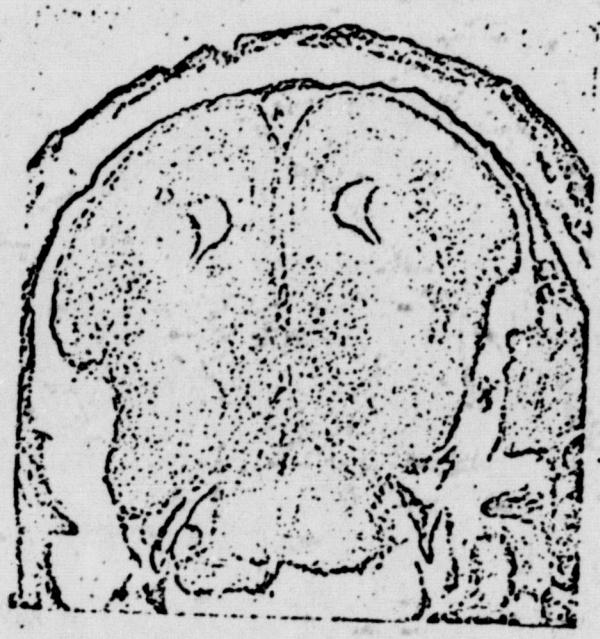


PLATE 3. Frontal section of abnormal head through optic chiasm, showing no optic fibers on left since microphthalmic eye had no optic nerve. (Approximately × 30)

PLATE 4. Abnormal right eye, filled with thick retina and showing no lens, iris, pupil, cornea, anterior chamber, or ciliary body. This eye had an optic nerve. (Approximately × 70)

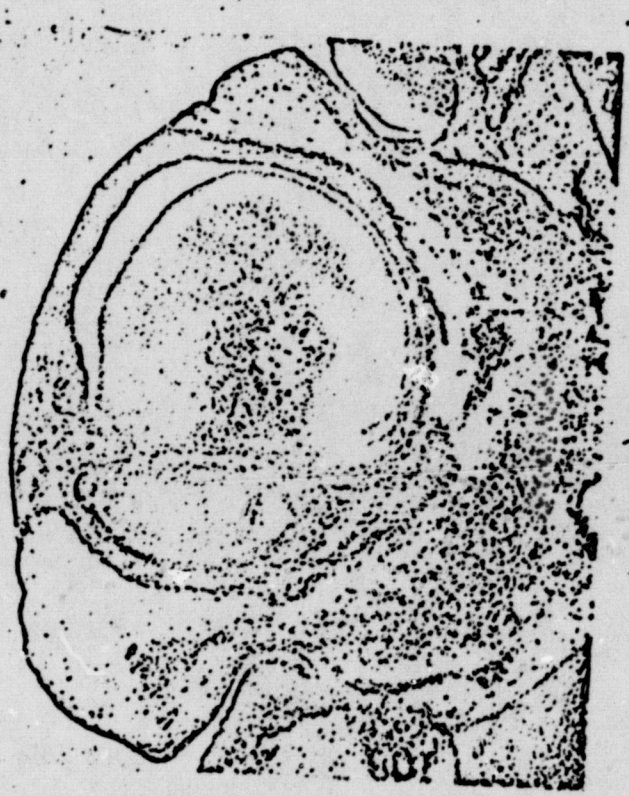


PLATE 5. Aphakic eye, showing extensive retinal coloboma. (Approximately × 73)

PLATE 6. Retinal coloboma of the type seen in almost all eyes of 45 serially sectioned offspring from pregnant mice given a large dose of vitamin A. In this defect, the lens has never been involved or even of less than normal size. (Approximately × 84)

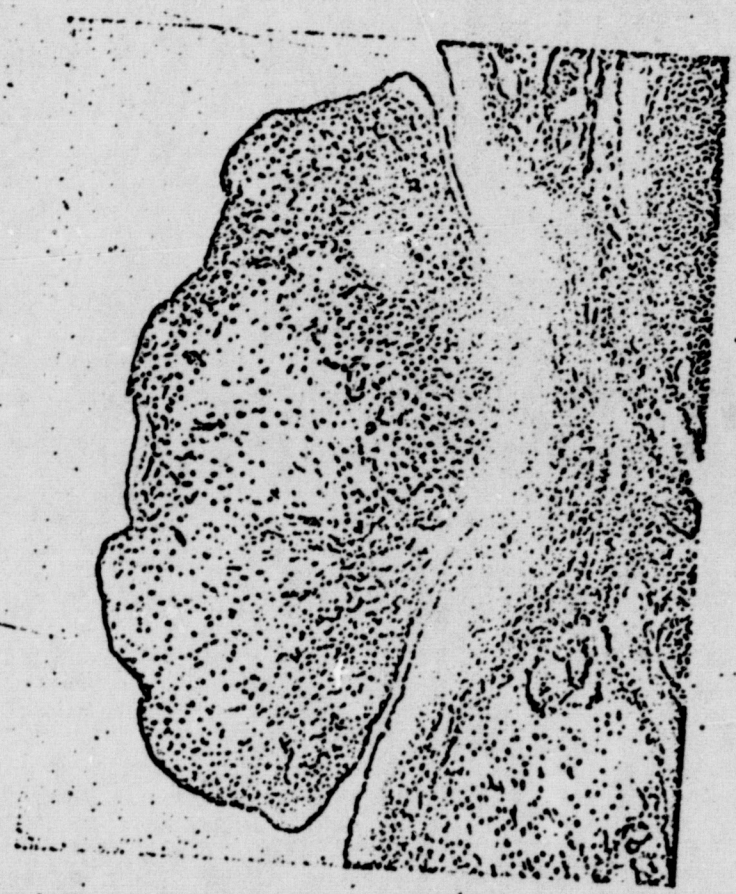


PLATE 7. Loosely filled sac projecting outward from aphakic eye, possibly representing or containing remnants of extruded lens. (Approximately × 85)

the optic chiasm. No optic fibers are present on the left side. Microphthalmia and absence of the optic nerve have been encountered repeatedly in experimental mammalian teratogenesis (Kalter and Warkany, 1959).

The right eye, however, presented a type of malformation that it is believed has not been previously reported as induced in mammals. The eye was represented by a vesicular structure almost entirely composed of a thick retina and contained none of the structures of the anterior segment, i.e., lens, iris, cornea, anterior chamber, pupil and ciliary body (Plate 4). The retina showed an extensive coloboma (Plate 5), and into the cleft, filling the cavity, there ran a thick band of tissue that was continuous with the circumferential mesodermal layer (Plates 4 and 5).

In 45 serially sectioned offspring from a group of females given an excess of vitamin A this was the only specimen with microphthalmia or aphakia. However, one other eye defect that occurred in almost every animal was retinal coloboma alone (Plate 6), which was of the sort called "typical" by Mann (1957), following as it does the line of the normal fetal fissure. Hence it may be conjectured that in the present case there occurred an exaggeration of the retinal defect commonly found; that the extreme abnormalities noted were secondary consequences of this severe form of retinal maldevelopment and overgrowth; and that the aphakia was probably the result of extrusion of the lens, remnants of which may be present in the loosely filled sac that projected outward from the eye (Plate 7).

This abnormality, occurring in an eye of approximately normal size, may thus be an instance of secondary destruction of the lens and a part of the picture of severe total retinal coloboma. As such, this lens defect is quite different in origin from the secondary aphakias cited by Mann (1957) and by Duke-Elder (1963) as occurring in human beings, since in those cases the defect appears to have been intrinsic to the lens.

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BIOMETRIC ANALYSIS OF THE EFFECT OF ORAL VITAMIN A ON HUMAN EPIDERMIS*

HERMANN PINKUS, M.D. AND ROSIE HUNTER

In a previous paper Hunter and Pinkus (1) reported that the oral administration of 150,000 units of vitamin A daily for one month decreased epidermal keratin cell counts in all of ten healthy volunteers. The question of the biologic mechanism that brought about this decrease is the subject of the present paper.

MATERIAL AND METHODS

Ten healthy adults (7 male and 3 female) ranging in age from 25 to 40 years volunteered for the study. The keratin layer was stripped off an area approximately 6 × 1.25 cm on the flexor surface of one forearm by repeated application of Scotch Tape® until a dry glistening surface was obtained. The stripped-off material was saved for counting horny cells as reported (1). Under local xylocaine anesthesia, 2 mm punch biopsy specimens were removed from the stripped area 24, 48, 72, and 96 hours later (Series 1), and a control specimen was taken from normal skin at least 2 cm distant to avoid spill-over of mitotic activation (2). The subjects then took one buccal dose of vitamin A, 150,000† units daily for 30 days. A similar area was stripped on the other forearm at the end of this period, and control and 24, 48, 72 and 96 hour biopsy specimens were taken (Series 2). A final strip and third series of specimens were done at the end of another month during which no vitamin A was taken.

The specimens were fixed immediately in formol alcohol and embedded in paraffin. Cells were counted in serial sections cut at 8μ and counts corrected according to Abercrombie's formula as described by Pinkus (3). The number of resting and dividing nuclei was determined for one square millimeter. The number of horny cells per square centimeter was taken from published data (1) and divided by 100.

RESULTS

The experiment had two parts and two purposes.

A. Control biopsy specimens of each of the three series combined with counts of stripped-off horny (keratin) cells furnished information on possible effects of vitamin A on skin in its normal, "static" condition.

B. Specimens taken after stripping measured the ability of the epidermis to restore the lost keratin layer under the influence of vitamin A.

Table 1 lists corrected cell counts of one representative case.‡ All other data have been summarized in graphs in which the values of the control specimen of Series 1 are set at 100%. This was done to eliminate considerable variations of initial numbers of cells between individuals (Table 2). Because of this great variability of individual values, no statistical analysis was attempted. It may be mentioned that cell counts done by one experienced observer are reproducible with ±10% accuracy. Larger deviations may be considered significant.

A. Effect of vitamin A on number of epidermal cells.

Figures 1–8 represent percentage changes in the number of various classes of cells in the epidermis. As was shown in the preceding paper, the number of stripped-off horny cells (Fig. 1) was decreased in all 10 cases in Series 2 after one month of vitamin A, reversed the trend in Series 3, taken one month after vitamin A had been discontinued, in 7 cases and exceeded initial values in 4 subjects. It is seen in Fig. 2 that in contrast the number of all nucleated elements, including basal cells, prickle cells, granular cells, and often a few parakeratotic cells, was increased in 9 of the 10 cases in Series 2. The trend was reversed in 7 of these 9 subjects in Series 3, but remained above initial values in 6. The 10th subject (Case 6) showed a smaller number of nucleated cells in Series 2 and remained below the control value in Series 3. There was no apparent explanation except that his initial cell count had been unusually high and actually exceeded values found in some of the other subjects in Series 2.

By adding the figures for stripped-off horny

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† Vi-Dome-A Oral Tabs® were supplied by Dome Chemicals Inc., N.Y.C.

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‡ Complete data may be obtained from the authors on request.

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TABLE 1

Corrected cell counts of Case 3 per square millimeter

Phase of Experiment	Time after Stripping	Basal Cell Nuclei	Prickle Cell Nuclei	All Intermitotic Nuclei	Keratohyalin Nuclei	Parakeratotic Nuclei	All Postmitotic Nuclei	All Nuclei	All Mitoses	% of Intermitotics
Initial, Series 1	Control	15,000	34,300	49,300	5,100	100	5,200	54,500	20	0.011
	24 hrs	11,700	24,100	35,800	6,300	16,400	22,700	58,500	120	0.340
	48 hrs	13,200	32,900	46,100	13,600	14,200	27,800	73,900	1,600	3.470
	72 hrs	18,400	52,400	70,800	14,300	13,600	27,900	98,700	1,575	2.230
	96 hrs	13,400	29,900	43,300	9,900	16,400	26,300	79,600	178	0.410
One month, Series 2	Control	23,800	51,300	75,100	4,400	200	4,600	79,700	133	0.180
	24 hrs	14,100	33,600	47,700	6,100	6,400	12,500	60,200	0	0.000
	48 hrs	12,600	30,400	43,000	17,600	9,400	27,000	70,000	891	2.072
	72 hrs	13,900	34,000	47,900	9,300	4,500	13,800	61,700	280	0.584
	96 hrs	16,800	42,800	60,600	13,200	8,400	21,600	91,200	120	0.172
Two months, Series 3	Control	16,000	43,700	59,700	7,000	300	7,300	67,000	29	0.049
	24 hrs	15,000	37,400	52,400	5,900	8,100	14,000	66,400	50	0.095
	48 hrs	14,900	28,900	43,800	22,100	23,600	45,700	89,500	2,171	4.956
	72 hrs	15,300	41,700	57,000	14,600	26,300	40,900	97,900	444	0.778
	96 hrs	12,900	29,400	42,300	10,800	30,700	41,500	83,800	422	0.998

cells per square mm to the sums of all nucleated cells counted in sections, an approximate value is obtained for all cells per square mm of skin surface. Fig 3 shows that these values fluctuate less, are close to initial figures in 4 cases, definitely higher in 5, and lower only in the exceptional case 6. The generally higher counts in Series 2 are due to the fact that the number of prickle cells which account for the main mass of the epidermis is elevated in 9 cases (Fig. 6). Basal cells (Fig. 5) and post-mitotic cells (granular plus parakeratotic cells, Fig. 8) are more numerous in 7 cases. Most cell counts show a tendency to return closer to initial values at the end of the second month (Series 3), except the granular cells which are widely scattered and mostly elevated.

B. Effect of vitamin A on forced regeneration after stripping.

Stripping-off the keratin layer produces a predictable mitotic burst in normal human epidermis as shown by us (2, 3) and others (4). Highest mitotic counts usually are found 48-72 hours after stripping and may reach 4-5% of intermitotic (basal and prickle) cells. Cell division usually takes place in the basal layer and the one immediately above (suprabasal). In this series of experiments, peak mitotic counts of 3% or more were encountered initially in 8 cases (Fig. 9). The remaining 2 showed peaks of only 1 and 1.5%, and one of these, a 38 year old female subject, had even lower counts in Series 2 and 3 without deviating from the average in other respects.

TABLE 2

Cell counts (per square mm) in control specimens before vitamin A (Series 1)

Case Number	Basal Cells*	Prickle Cells*	All Postmitotics*	All Nucleated Cells*	Keratin Cells†
1	14,800	35,300	7,000	57,100	17,200
2	15,300	26,600	8,000	49,900	14,000
3	15,000	34,300	5,200	54,500	13,600
4	16,500	33,800	11,300	61,600	13,300
5	14,900	30,300	6,000	51,200	11,600
6	18,800	41,700	6,900	67,400	11,200
7	16,800	34,100	9,800	60,700	10,900
8	17,400	32,900	8,400	58,700	10,900
9	18,100	33,000	6,900	58,000	10,600
10	12,800	29,300	8,900	51,000	8,600

* Counted in paraffin sections.

† Counted in tape strips.

Peak mitotic counts were lower in Series 2 in 7 subjects, higher in 3. This trend reversed itself in Series 3 in 6 (3 up, 3 down) and was farther down in 4. Because of the possibility that the mitotic effort may have been lower at any one time, but more prolonged after vitamin

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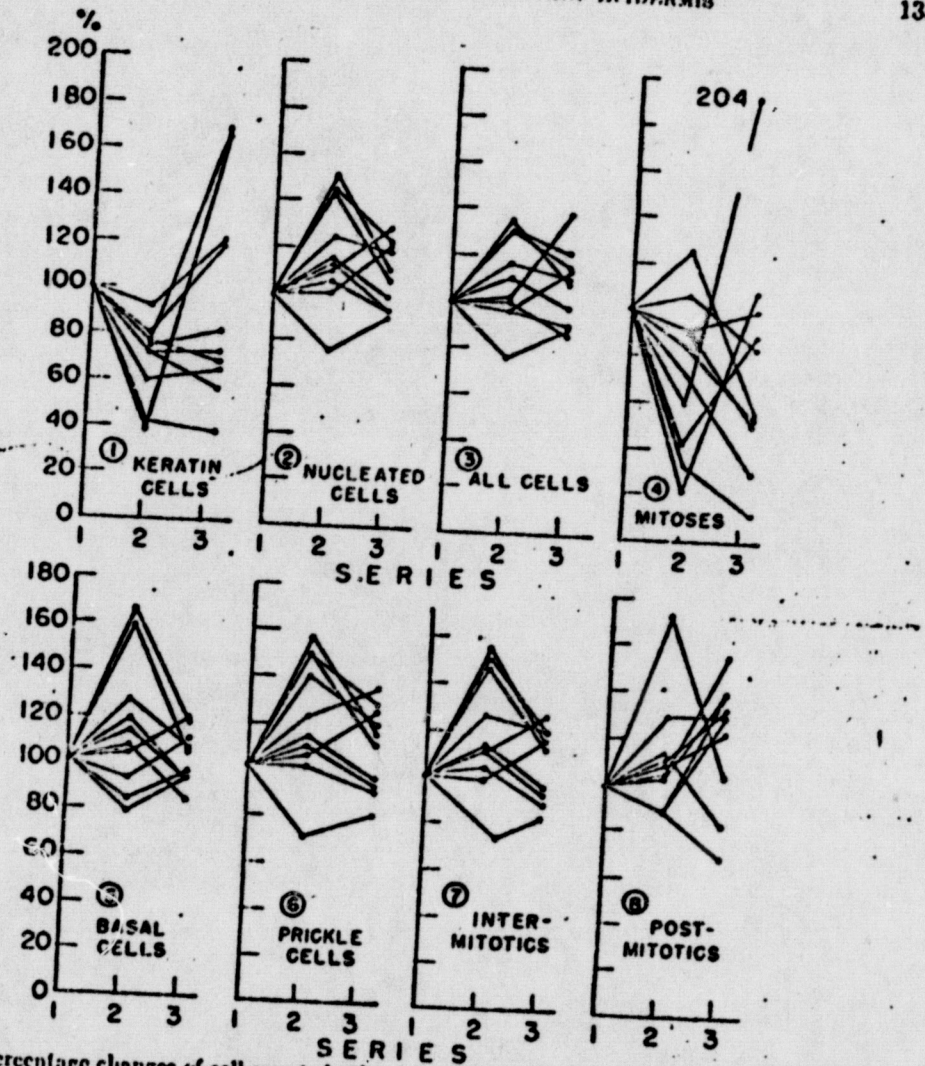

FIGS. 1-8. Percentage changes of cell counts in the three phases of the experiment. All initial values (Series 1) given as 100% norm. Series 2 shows values in the control specimens taken after one month on vitamin A. Series 3 shows values at the end of the second month, 30 days after vitamin A was discontinued. Horny cells were counted in strips, nucleated cells in paraffin sections.

A, the sum of all mitoses seen in the 5 specimens of each series was obtained. This did not change the overall result as evidenced by the fact that 7 subjects had lower total counts and 3 had higher values in Series 2. Mitotic peaks were lower in Series 3 than in Series 1 in 7 subjects, total counts also lower in 7 subjects.

DISCUSSION

From the rather bewildering diversity of individual responses, three facts stand out as probably having some significance.

1) After one month of a daily dose of 150,000 units of vitamin A, the number of horny cells that could be stripped from a given area was decreased in all 10 subjects.

2) The number of nucleated cells in a similar area was increased in 9 of the 10.

3) The mitotic response to stripping was decreased in 7, definitely higher in only 1 subject of the 10.

It must be emphasized in discussing these results that we are not concerned with statistical

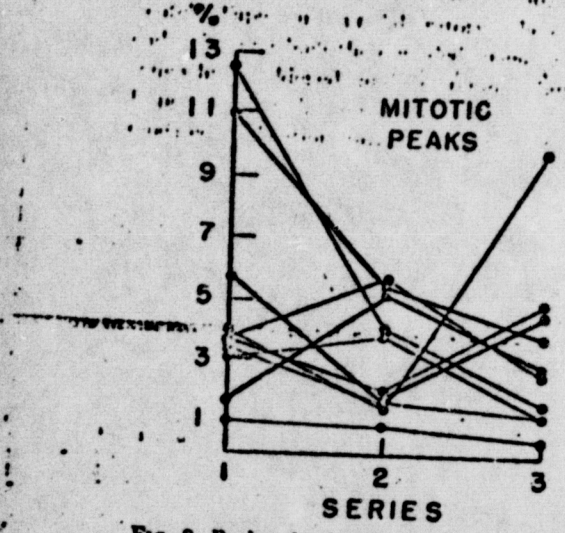

FIG. 9. Peak mitotic counts expressed as per cent of intermitotic (basal plus prickle) cells in Series 1, 2 and 3.

significance, but are content to point out trends. It seems then that there is no overall decrease of cells in the epidermis, rather a shift from fully keratinized cells to less mature forms in the majority of cases. Basal cells, prickle cells, and granular cells have a tendency to increase in percentage under the influence of vitamin A, although this trend is not consistent. The data seem to support the often voiced view that vitamin A has an "antikeratinizing" effect and suggest that this is achieved by cells remaining immature longer. Total cell counts remained the same or were somewhat higher. Thus, there is no evidence that vitamin A in the doses and during the time of our experiment led to general epidermal atrophy. Visual examination of representative control sections of the three series show that the epidermal cells look somewhat larger and more succulent in Series 2 (Fig. 10 A-C.)

Another point that is obvious in sections of most 24 hour specimens of Series 2 is the somewhat less complete denudation of the surface. This observation is at once disturbing and revealing. When epidermis is stripped with Scotch Tape® in our laboratory, there is an end point at which the denuded surface appears somewhat reddened and glistening, but dry. Experience has shown us that from this point on, repeated applications produce very few additional cells, that stripping comes to a natural end. The most likely reason is that the more cohesive and somewhat moister granular cells do not adhere to the pressure sensitive tape. Our experience in this respect differs from that of some other authors who have stated that they can strip off living epidermis and produce a moist and even bleeding surface with the tape they have used. While we do not question these results, we state that stripping with the ordinary brand of Scotch Tape® in our hands leads to a rather sharp end point in gross clinical observation. It seems, however, that histologically this end point changes slightly under the influence of vitamin A. It may be that the youngest (lowest) horny cells are more cohesive and perhaps more moist, or it may be that in the first 24 hours after stripping, new keratin cells are quickly produced by the hypertrophic granular layer. The latter possibility is less likely as no definite decrease and often an increase of granular cells was observed between the control and the 24 hour specimens.

In any case, since the entire number of horny cells is not more than 15-20% of the total number of epidermal cells in any of our subjects, the few cells left on the skin surface in Series 2 (and therefore not counted) do not materially influence our conclusions concerning the number of cells.

The next point for discussion is the restitution of the keratin layer after stripping and the mitotic effort that is responsible for it. Neither microscopic examination nor differential cell counts suggested any impairment of the ability of the epidermis to keratinize. On the other hand, the mitotic effort seemed to be somewhat less vigorous under the influence of vitamin A. This does not imply changes in the normal turnover of the epidermal cells. This process is slow and our counts did not reflect any changes. However, under the conditions of forced regeneration after stripping, the majority of subjects exhibited lower mitotic peaks and lower total number of mitoses.

It is known, especially through the work of Bullough (5) that lifespan of keratinocytes and mitotic activity are reciprocally connected. Not only does increased mitosis lead to faster exfoliation (shorter lifespan), but factors leading to decreased exfoliation inhibit mitosis. It is tempting to assume that the retarded maturation of keratinocytes that is suggested by our figures is

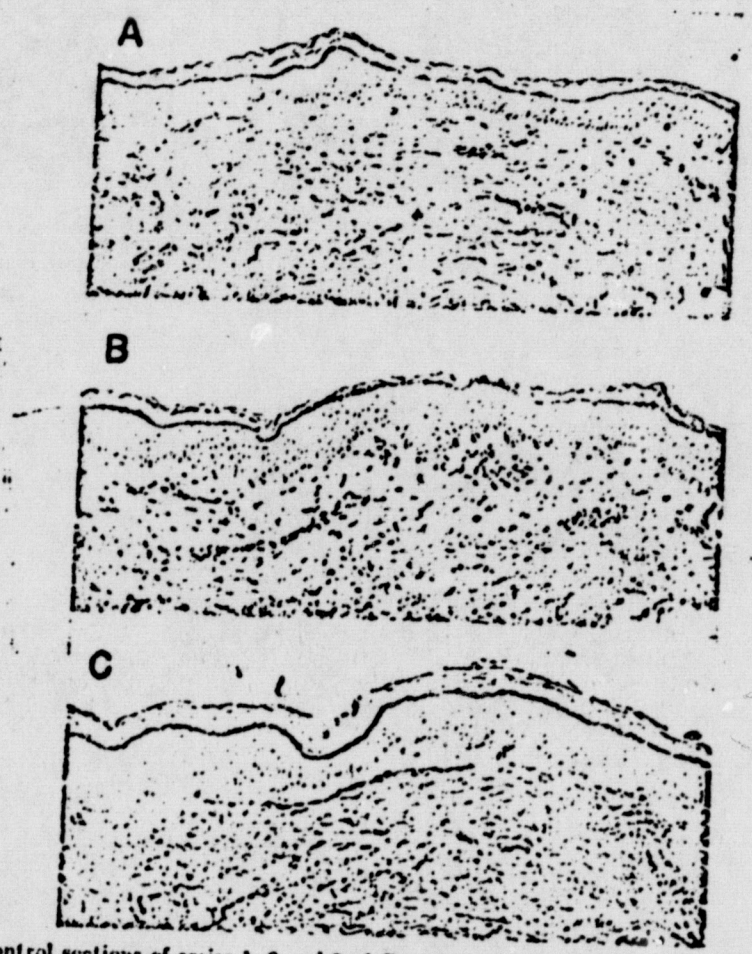

FIG. 10. Control sections of series 1, 2 and 3 of Case 9, stained with H & E, 90 ×. A: Initial stage before vitamin A. B: After one month of vitamin A. C: One month after discontinuing vitamin A.

responsible for the decrease of regenerative activity. However, Pinkus showed in his first experiments (3) that the force of regeneration is directly proportional to the completeness of denudation. It is possible therefore that the somewhat less complete stripping in Series 2 is responsible for the lessened mitotic vigor, and that this is not due to a direct metabolic effect of vitamin A.

SUMMARY

Daily administration of 150,000 units of vitamin A for one month in the form of buccal tablets to 10 adult volunteers produced the following effects on the epidermis:

1) The number of horny cells that could be stripped off a unit area by pressure-sensitive tape was decreased in all ten subjects.

2) The number of nucleated cells per unit area of skin surface was increased in nine subjects.

3) Total number of cells (nucleated plus non-nucleated) was moderately increased in six subjects.

4) Mitotic effort after denudation by tape stripping was somewhat less vigorous in seven subjects and slightly elevated in three. It seems possible that the decrease is due to less complete stripping of vitamin A-influenced skin rather than to a direct metabolic effect.

5) Vitamin A in the doses administered appears to have a retarding effect on the maturation of human keratinocytes.

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LVIS DETECTION OF TERATOGENIC ACTIVITY

The Rapid Detection of Teratogenic Activity

The Rapid Detection of Teratogenic Activity*

Vergil H. Ferm, M.D., Ph.D.

The need for a rapid and reliable test for the teratogenicity of drugs, chemicals, and certain metabolic procedures in mammals has become quite apparent. While it is difficult to conceive of a test that will screen all compounds for possible teratogenic activity in any mammal, this report will indicate that consistent teratogenic effects can be noted within 24 hours following the administration of known teratogens to the pregnant golden hamster. There is little quantitative data on the effects of teratogenic agents on the young mammalian embryo, and the frequency and degree of malformations prior to the *in utero* death and resorption of the severely malformed embryos are not known. Studies on the presomite, preimplantation blastocyst of the rabbit have revealed the sensitivity of this structure to various chemical agents,[1] but these data do not give any information on the organogenesis of embryonic malformations. No claim is made that the present study represents a universal answer to the need for a mammalian teratogenic screening procedure; however, it does represent a simple, fast, and economical method which bears further investigation.

The golden hamster possesses a remarkably short gestation period of 16 days, reproduces in a manner making it possible to obtain timed matings easily and accurately, and has large litters, thus aiding in the interpretation of the embryonic responses to teratogens. In addition, the golden hamster has responded to a known group of chemical teratogens such as: trypan blue,[4] colchicine,[5] Vinblastine,[6] Vincristine,[6] vitamin A,[13] 5-bromodeoxyuridine,[14] salicylamides,[15] as well as to teratogenic viruses (H-1),[8] and certain other procedures (freezing,[16] hyperbaric oxygen,[7] irradiation[9]).

For those experimental teratogenic procedures used by the present author, the eighth day of gestation in the hamster was found to be optimal for induction of teratogenic effects. The telescoping of the critical periods of embryogenesis necessitated by the short gestation period makes it possible to examine grossly the developing embryos on the ninth day of gestation, 24 hours after administration of a teratogenic insult.

MATERIALS AND METHODS

Young virgin female hamsters (*Cricetus auratus*) were caged individually and maintained on Purina laboratory chow. During the early evening hours individual females were placed into the cage of a breeder male and observed for a few minutes. If in estrus, the female assumed a characteristic lordotic stance, remained stationary, and accepted the male. If not in estrus, the female would resist the male and continually investigate the new environment. When breeding occurred, the female was left with the male overnight and removed, early the next morning, to her individual cage. The night when the pair were placed together is considered to be "day 0" of pregnancy and the day of separation is considered to be "day 1" of pregnancy. The bred females were maintained on laboratory chow until used.

On the eighth day of gestation the females were weighed and anesthetized with intraperitoneal Nembutal (6.5 mg. per 100 gm.). Maternal weights ranged from about 100 to 125 gm. Various known teratogenic compounds were injected directly into the lingual vein and the animals returned to their cages. Control animals were injected intravenously with 1.5 ml. of normal saline. Vitamin A was administered by stomach tube without anesthesia. The following procedures have been employed in the present investigation: (1) controls, 1.5 ml. of normal saline intravenously; (2) 5-bromodeoxyuridine, 400 mg. per kg. intravenously; (3) colchicine, 10 mg. per kg. intravenously; (4) trypan blue (see Table 1); (5) vitamin A, 20,000 units by gavage.

The animals were sacrificed 24 hours later with ether, and the uterus, containing the gestation sacs, delivered into a Petri dish containing physiologic saline. Each gestation sac was then opened with fine dissecting instruments, and the yolk sac placenta and amnion dissected away from the embryos. The embryos were delivered into another dish with saline by means of a glass pipette. Observations were made on all embryos and the presence of cardiac activity was noted. The embryos were then placed into alcohol-formalin-acetic acid fixative prior to photography.

RESULTS

With care and patience it is possible to recover over 90 per cent of the embryos of each litter even though the average crown-rump (C-R) length of control embryos recovered on the ninth day of gestation is about 3.5 mm. Approximately 80 per cent of the embryos recovered in this study showed evidence of cardiac activity which persisted for some 10 to 15 minutes after removal from the gestation sac at room temperature. Remarkably few of the gestation sacs were completely empty and it was almost always possible to identify the embryonic tissues.

In this study, only external malformations were sought. These included craniochisis (Figs. 1, 3, and 5), spina bifida (Fig. 4), ectopic heart, microcephaly (Fig. 4), severe growth retardation, and abnormal facial development.

Table 1 summarizes the results obtained from the control and experimental groups. Without attempting to list all the malformations noted in each group, it was noted that, in general, the colchicine group had the most severe malformations, represented by marked distortion of the anterior neural tube and head (Fig. 2). Recovered

TABLE 1. EFFECT OF 24 HOUR EXPOSURE TO TERATOGENS ON EMBRYONIC DEVELOPMENT IN THE GOLDEN HAMSTER

	No. of mothers treated	No. of embryos recovered	No. of abnormal embryos
Controls	5	55	0
Colchicine	7	60	36
Vitamin A	26	220	140
Trypan blue*	9	95	42
5-Bromodeoxyuridine	4	33	18

* Two animals, 0.5 ml. of 0.1 per cent, intraperitoneally; four animals, 0.5 ml. of 0.1 per cent, subcutaneously; three animals, 0.5 ml. of 0.1 per cent, intravenously.

embryos were noticeably smaller in the colchicine-treated group than in the other groups. Administration of trypan blue commonly induced exencephaly and bifida; the route of administration 1) had no apparent effect on the incidence or type of abnormalities found. Vitamin A-induced anomalies were generally confined to the head and consisted of an open and flared neural tube in this region (Fig. 5). One entire litter of 13 embryos from a mother treated with vitamin A exhibited this same defect. Animals treated with 5-bromodeoxyuridine showed the greatest variety of cranial abnormalities (Fig. 3), ranging from microcephaly to a marked dilation of the brain region possibly representing an early hydrocephalus.

An unusual malformation was found in one of the litters whose mother received vitamin A. Twins, conjoined laterally at the thoracic level (thoracopagus), were removed from one gestation sac (Fig. 6). These twins were equal in size and both showed the same degree of craniochisis. No similar examples of this malformation have been noted in this laboratory in several hundred hamster pregnancies studied.

DISCUSSION

Embryonic development in the hamster proceeds in a rapid manner which is quite striking during the eighth day of gestation. Gestation sacs opened early (8 a.m.) on

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FIG. 1. Normal 9 day-old embryo removed from a control mother. C-R length, 3.5 mm. ×18.

FIG. 2. Embryo, 9 days old, from mother receiving 10 mg. per kg. of colchicine intravenously on the eighth day of gestation. Note markedly enlarged and dilated cranial end of embryo, presumably representing an early hydrocephalus. ×16.

FIG. 3. Hamster embryo, 9 days old. Mother received 400 mg. per kg. of 5-bromodeoxyuridine on day 8. Marked craniochisis and early exencephaly. Tail has been inadvertently removed. ×17.

FIG. 4. Embryo, 9 day. old, from mother receiving 0.5 ml. of 0.5 per cent trypan blue intravenously 24 hours previously. Note moderate exencephaly and double spina bifida (arrows). Cardiac activity noted at time of recovery. ×20.

the eighth day revealed an embryonic disc stage (1 to 2 somites) with an over-all measurement of approximately 1.5 mm. by 1.0 mm. The first cardiac activity is noted later on the eighth day (3 p.m.). Development proceeds within the next 24 hours to reach the stage depicted in Figure 1, characterized by a functional heart, completely

FIG. 5. Litter mates removed on the ninth day of gestation following maternal feeding of 20,000 units of vitamin A 24 hours previously. Embryo at *upper left* is grossly normal. Others show varying degrees of malformations. ×10.

closed neural tube, visceral arches, optic and otic placodes, and beginning formation of limb buds. Thus the critical stage of embryonic response to teratogenic influences in this animal will fall within a very closely defined period. A comparable period of human development would extend from about the 21st to the 30th day of gestation.

Relatively little information is available on the incidence of congenital malformations in early mammalian development. In most experimental studies, a period of 1 to 2 weeks exists between the time of administration of a teratogenic insult and the recovery and study of the surviving fetuses. Mall,[11, 12] in a comprehensive study of spontaneous human abortuses, concluded that about 50 per cent of abortuses recovered during the first 2 months of pregnancy were abnormal, and that two-thirds of these were first month specimens. Recently, the high incidence of chromosomal abnormalities[2, 3] found in early human abortuses adds further evidence to the fact that a surprisingly high number of early human embryonic specimens are abnormal.

In the evaluation of the potency of any single teratogenic stimulus, three main factors need to be considered. The first of these is the intensity with which one looks for malformations. In the present study it is highly probable that histologic study of the grossly normal appearing embryos by serial section would have revealed further evidence of malformations in internal organ systems. Furthermore, in the natural history of the development of congenital malformations, it is apparent that certain malformations are secondary to some primary defect and would not have had time to maldevelop at this early stage. The obvious examples of this situation are the rib defects commonly seen in colchicine[8] and vitamin A[13]-treated hamsters which are examined much later in gestation after formation of the bony skeleton. The primary defect here is probably related to grossly undetectable but histopathologic changes in the embryonic somite.[13] Both of these first two factors, then, would tend to lower the estimate of the actual effectiveness of the teratogens used in this study. This also emphasizes the fact that the

evaluation of those teratogens whose only effect may be upon those organ systems

Pregnant hamsters were treated with

H-1 virus. *Science 125:* 310, 1964.

Kerbel, F. and Mall, F. P., Vol. 1, p. 30; Philadelphia, J. B. Lippincott Company, 1910.

reaching full development at a later stage of development.

Finally, the potency of a teratogenic agent may not be fully evaluated unless a search for malformations is made early in development before the more seriously affected embryos die *in utero*, undergo resorption, and are lost as far as statistical teratogenic data are concerned. The fact that these fetal resorption sites, discovered late in gestation, probably represent malformed fetuses is generally assumed, but until attempts to study these early effects of teratogens are made, the full range of malformations due to a single compound will not be known. These findings now permit an approach to the sequential morphogenetic study of selected malformations.

FIG. 6. Conjoined twins of 9 days gestational age from mother receiving vitamin A 24 hours previously. Each twin has an open anterior neural tube. ×30.

various known teratogens on the eighth day of gestation. The embryos were recovered 24 hours later by careful dissection, examined, and photographed.

Intravenous injection of the pregnant mother with colchicine, 5-bromodeoxyuridine, and trypan blue, as well as the oral feeding of vitamin A, induced clearly recognizable aberrations of development at the end of the 24-hour period as compared to normal controls. These malformations consisted of craniochisis, spina bifida, microcephaly, hydrocephalus, and marked growth retardation. An unusual case of conjoined twins was found in one litter whose mother was treated with vitamin A.

Since many of the more severely malformed embryos would presumably die in *utero*, undergo resorption, and thus be excluded from statistical teratogenic data, it is suggested that this method would not only be a rapid method for the evaluation of the teratogenic potential of particular agents, but it would also give some true indication of the degree and range of malformations resulting from a teratogenic insult.

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Malformations of the Mouse Fetus Caused by Hypervitaminosis-A of the Mother During Pregnancy

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Introduction

A TERATOGENIC effect of hypervitaminosis-A upon the rat embryo was reported by Cohlan in 1953.[3] Giroud and Martinet (1955-59)[5,6] extended the study. Woollam and Millen (1957-61),[10,26,27] and Millen (1962)[16] also carried out similar experiments in the rat. Using rodents, Deuschle, Geiger and Warkany (1959),[9] and Kalter (1960)[11] have described the occurrence of visceral changes. In Japan, Baba and his collaborators (1958-1960)[1,2,9,23] and Takekoshi (1961)[21,22] studied the effect of hypervitaminosis-A upon the fetus of the rat and mouse. Authors of the present paper carried out experiments in the mouse using hypervitaminosis-A of the mother during pregnancy. As a result, there were many fetal malformations of the same type previously described in the literature. Among such malformed fetuses were many showing a certain combination of defects called the oculoalentofacial pattern by Deuschle et al, as well as apparent micromelias. This paper stresses these unique patterns due to hypervitaminosis-A.

Methods

Animals used in these experiments were of the ddN and CF_1 strains of mice, originally supplied by the Zikkenbobutsu Chuo Kenkyujo, Tokyo (Central Laboratories for Experimental Animals), 90 days or older, and weighing an average of 34 gm. In each case, one estrous female was kept overnight in a cage with one male. The next morning, all the females having a vaginal plug were considered to be in the first day of pregnancy. The pregnant mice were divided into six groups, ie, group A8 corresponding to the 8th day of pregnancy, group B 9 to the 9th, group C 10 to the 10th, group D 11 to the 11th, group E 12 to the 12th, and group F 13 to the 13th day. Each group contained 20 animals. The control group had ten animals.

Each test animal was given a single, intraperitoneal injection of 15,000 international units (IU) vitamin A water miscible solution. Experiments employing the ddN strain of mice were done as a pilot study; results will be published elsewhere (Kameyama and Murakami, 1964).[12]

Fetuses were removed surgically from mother animals on the 19th day of pregnancy and examined under a low power microscope for gross malformations. All fetuses were reexamined under the same binocular after being processed by the Dawson method of clearing tissues with one percent potassium hydroxyde solution and staining bones with alizarin red S solution.

Besides the above groups of animals, the fetuses of some mice treated on the 9th day of pregnancy were examined for changes in craniofacial patterns on the 15th and 16th days of pregnancy in sections stained with hematoxylin and eosin.

Results

As shown in Table 1, in each group administered vitamin A the mean litter size was smaller than in the controls. Group A 8 showed the most effect and embryonic and fetal deaths including resorptions and placental remnants

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Designation and Day of Pregnancy Treated	Number of Treated Mice	Total Number of Conceptuses	Total Number of Fetuses	Mean Litter Size	Intrauterine Mortality: Dead Fetuses	Intrauterine Mortality: Resorptions—Remnants	Fetuses Without Gross Malformations	Fetuses with Gross Malformations	Fetuses Retarded in Development
A-8	20	191	15	0.8	1 (0.5%)	175	0	15 (100%)	6 (40.0%)
B-9	20	177	149	7.4	1 (0.6%)	26	0	149 (100%)	12 (8.1%)
C-10	20	208	143	7.2	30 (20.6%)	69	12 (8.4%)	131 (91.6%)	21 (16.1%)
D-11	20	185	160	8.0	8 (5.0%)	17	15 (11.0%)	143 (89.0%)	20 (13.7%)
E-12	20	170	157	8.4	8 (5.1%)	7	22 (15.7%)	135 (84.3%)	15 (11.1%)
F-13	20	195	182	9.1	8 (4.7%)	11	143 (78.6%)	39 (21.4%)	3 (2.1%)
Untreated control	10	111	102	10.2	0	0	105 (94.6%)	2 (2.0%)	0

totalled 176 or 92% of all conceptuses. The 15 fetuses which were alive had gross malformations. In group B 9, the incidence of embryonic and fetal deaths was only 16%, but all living fetuses were malformed. In group C 10, the frequency of embryonic and fetal deaths reached nearly 30%, and 92% of living fetuses were malformed. In the three remaining groups which were treated on or after the 11th day of pregnancy intrauterine mortality rates approximated control levels but the frequency of gross malformations remained at high levels of 89%, 81%, and 21% respectively.

Among gross malformations, two cases each of exencephalia were found in group A 8 and B 9—the frequency was 13.33% in group A 8 and 1.33% in group B 9. There were two cases or 13.33% of spina bifida aperta (Fig 7A) in group A 8, but the defect was also detected in groups C 10 and D 11, although the incidence was very low (Table 2). Many microcephalic fetuses were seen in group B 9. However, the defect was not simple microcephalia, but was usually associated with other malformations as described later (Fig 1 and 7B). Malformations of the eye for the greater part were exophthalmoses manifested following treatment on the eighth or ninth day of pregnancy (Fig 2 and 7B). In almost all cases the eyelid was open. Cases of micro- or anophthalmoses were few (Table 2). Malformations of the jaw and mouth were manifested in fetuses treated on the eighth and ninth day of pregnancy. Micrognathia, agnathia and microstomia were usually associated with microtia. Anotia, and abnormalities of the auricle such as absence, lobulations, or dislocation were also associated with the above malformations (Fig 3 and 7B). Fetuses with such complicated malformations usually manifested microcephalia and exophthalmos with open eye. Such malformations were unique to experiments with hypervitaminosis-A. The incidence of cleft palate was highest (of the order of 70%) in middle pregnancy; the incidence was reduced somewhat in groups B 9 and F 13

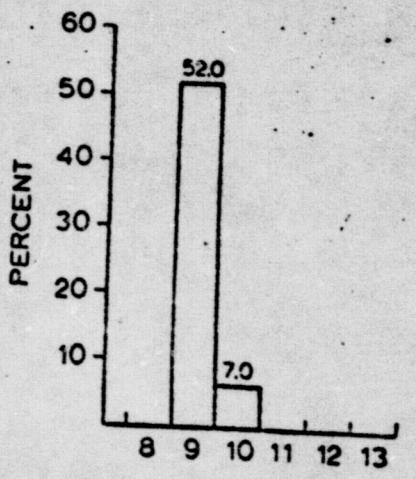

Fig 1.—Rates of microcephalia by day of pregnancy on which vitamin A was administered.

the high incidence of microstomias and anostomias made it difficult to inspect the

Malformation Classification		Day of Pregnancy When Treated						
		8th (Group A)	9th (Group B)	10th (Group C)	11th (Group D)	12th (Group E)	13th (Group F)	Control
CNS	Exencephalia	2(12.50 %)	2(1.36 %)					
	Brain hernia							
	Hydrocephalus			1(0.7 %)				
	Microcephalia *			0(2.8 %)				
	Spina bifida		77(52.40 %)	10(6.99 %)				
Eye	Anophthalmia	2(12.50 %)		1(0.7 %)	2(1.64 %)			
	Microphthalmia	2(12.5 %)		6 (6.29 %)				
	Exophthalmos *			4				
	Open eye *	14(88.33 %)	105(72.97 %)	15(10.49 %)				
	Short snout	9(56.00 %)	65(44.20 %)	2(1.4 %)				
	Mandible malformations		84(55.70 %)	28(20.27 %)	17(13.43 %)	6(4.29 %)		
Face	Absent big		21	6				
	Incomplete		84 (81.70 %)	29 (21.45 %)	29(22.37 %)	6 (7.86 %)		
	Agnathia	1(6.67 %)	16	1		22		
	Mouth malformations							
	Microstomia	3 (75.33 %)	12 (81.70 %)					
		9	69	0(0.0 %)			0(0.00 %)	
	Anostomia							
	Auricula malformations							
	Microtia		29	9				
	Anotia	12(80.00 %)	25 (70.27 %)	(7.14 %)				
	Cleft palate		46	29	6(2.61 %)			
Trunk	Abdominal hernia		27(18.24 %) †	85(65.53 %)	122(91.86 %)	113(87.60 %)	32(36.13 %)	2(2.00 %)
	Anal atresia			3(2.1 %)				
	Talipes		27(18.24 %)	2(1.4 %)				
Tail	Short-tail	3 (85.00 %)	1 (60.84 %)	1 (26.07 %)				
	Curvature	0	25	42			13(7.28 %)	
			1	1				
Limb and digit	Forelimb malformations							
	Micromelia (higher grade)		12 (34.46 %)	72 (72.05 %)	88 (76.07 %)			
	Micromelia (lower grade)		20	29	29		0(0.00 %)	
	Forelimb digit malformations							
	Ectrodactylia							
	Brachydactylia	5(33.33 %)	12(8.78 %)	69(49.22 %)	13(11.30 %)	25(16.77 %)	2(1.1 %)	
	Syndactylia		24(17.67 %)	8(5.6 %)	10(8.13 %)			
			3(2.00 %)	23(17.66 %)	7(6.29 %)			
	Hindlimb malformations							
	Micromelia (higher grade)	2(13.33 %)	2 (32.40 %)	26 (81.70 %)	105 (71.17 %)	7 (60.13 %)		
	Micromelia (lower grade)		29	29	16	60		
	Clubfoot (excluding micromelia)	1(6.66 %)	3(2.00 %)	12(9.20 %)	6(5.46 %)			
	Hindlimb digit malformations							
	Ectrodactylia		0(0.66 %)	24(17.70 %)	103(83.19 %)	78(64.04 %)	2(1.1 %)	
	Brachydactylia			17(11.80 %)	6(7.46 %)	11(8.30 %)	5(1.40 %)	
	Syndactylia	1(6.66 %)	2(1.36 %)	24(6.70 %)	16(11.04 %)	9(6.6 %)		
	Annular groove of 5th digit				7(6.30 %)			

* These malformations were associated.

† Only 27 or 18.2 % of 148 fetuses could be examined for cleft palate, and all had the defect. The remaining fetuses had microstomia or anostomia and the palate could not be studied.

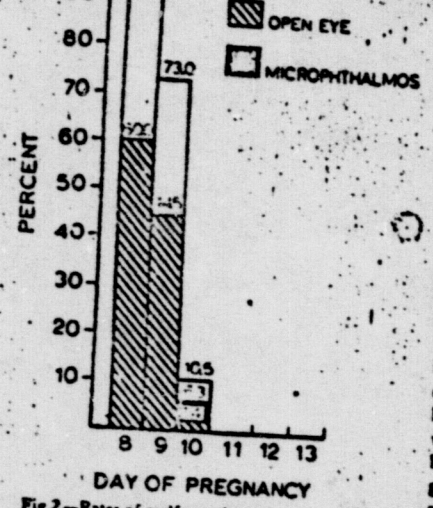

Fig 2.—Rates of malformations of the eye by day of pregnancy on which vitamin A was administered.

(about 18%) but was still 10 times greater than was to be observed among controls (Table 2, Fig 4). However, in group B 9, all fetuses could not be examined for cleft palate because

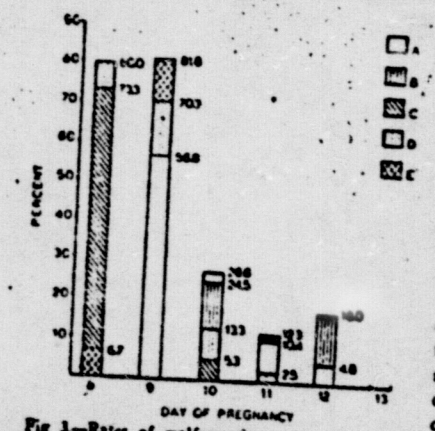

Fig 3.—Rates of malformations with craniofacial patterns by day of pregnancy on which vitamin A was administered. A, shortening of the snout; B, incomplete formation of the mandible and micrognathia; C, microstomia and anostomia; D, microtia, anotia, and dislocation of the auricle; E, agnathia.

the oral cavity; all 27 fetuses that were examined presented cleft palates. Also, in group B 9, there were 27 cases (18%) of anal atresia (Table 2). This malformation is one of the characteristic results of experiments using hypervitaminosis-A. The incidence of malformations of the tail was highest in group A 8—80%. In other groups, the frequency was gradually reduced as the embryo grew older (Table 2, Fig 5). There were many fetuses with noticable malformations of the extremities. The most prominent defects were micromelia and ectrodactyly (Table 2, Fig 6, 7C, and 7F). Both malformations were detected chiefly in groups C and D treated on the 10th or 11th day of pregnancy, respectively. The incidence was highest in group D. The incidence of micromelia in groups B 9 and C 10 was higher for the forelimb than for the hindlimb, while in group E 12 the incidence in the hindlimb was higher than in the forelimb. Also in group E 12 the frequency of ectrodactylism was much higher in the hindlimb than in the forelimb. The developmental stage at which the frequency of syndactylism was the highest was one day later for the hindlimb than for the forelimb.

In the skeletal system, characteristic changes were presented in the cranium, vertebrae, and extremities. In the cranium, remarkable deformities were detected chiefly in fetuses with craniofacial patterns such as microcepalia, hypognathia, micro- or astomia, micro- or anotia etc in groups A 8, B 9, and C 10. Each cranial bone, especially the frontal bone, was reduced in size and abnormally shaped. As a result, the head was formed small and abnormally shaped. The most marked change was in the zygomatic arch which was often incomplete, and the orbit formed was too shallow to hold an eyeball. In such fetuses the mandible was usually incompletely formed. In many cases only a rudiment could be detected or only the anterior part of the mandible was present, and even when the mandible was present, the posterior part was incompletely formed. These rudimentary mandibles were usually involved in an ankylosis, or fused with the maxilla or premaxilla (Fig 7D). The nasal and premaxillary bones were small, and the snout was short. Ossification of the tympanic bulla was usually absent. In histologic

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In these experiments with hypervitaminosis-A, the phenomenon called head-to-tail gradient shift of malformations in the vertebrae as demonstrated in previous experiments with hypoxia (Murakami and Kameyama, 1963)[19] or x-radiation (Murakami and Kameyama, 1964)[21] did not occur. In the group treated on the tenth day, malformations of lumbar vertebrae were marked, and seen in association with malformations of the tail. In the group treated on the 11th day, malformations were seen chiefly in upper cervical vertebrae. In the group treated on the 12th day, involvement of vertebrae apparently increased in frequency. Ribs are often involved in malformations of developing buds, and such involvement was also a characteristic in the present experiments (Fig 7E).

In the extremities, the long bones were involved in malformation and presented micromelia. The defects in the long bone ranged from slight curvatures to complete deficiency often associated with ectrodactylism. Cases in which the long bone was foreshortened were associated with thickening and curvature. In those with extensive involvement, the radius and the tibia were deformed in a corneous mass (Fig 7F).

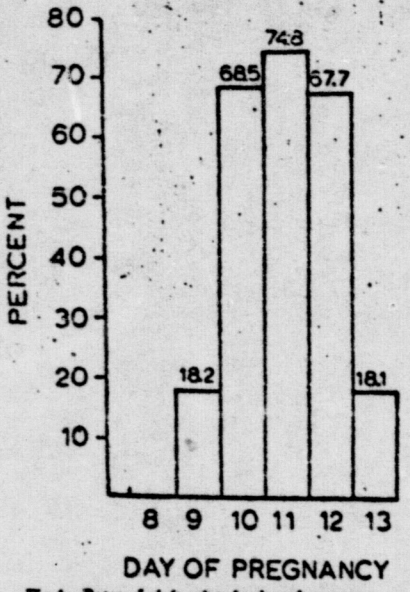

Fig 4.—Rates of cleft palate by day of pregnancy on which vitamin A was administered.

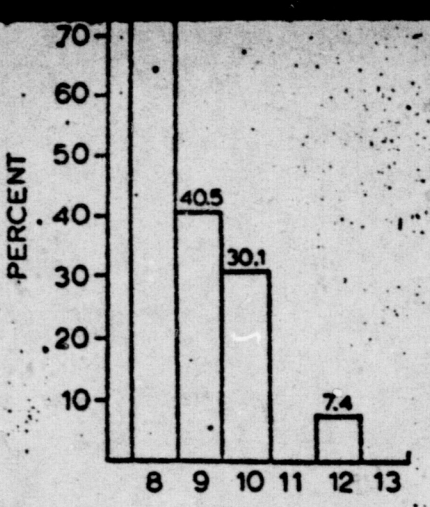

Fig 5.—Rates of tail abnormalities by day of pregnancy on which vitamin A was administered.

Among fetuses examined in histologic sections, there was a case with a rosette formation in the brain. It was formed in the mesencephalon from its superficial part to its surface in the form of a small tumor. The eye itself in exophthalmos was also abnormal and its longitudinal axis extended. This resulted in infolding of the posterior part of the retina. In fetuses with micrognathia, agnathia, microstomia, or anostomia, the palate was incompletely formed. In some, only a rudiment of the lateral palatine process was observable. In such instances, the tongue was also very small.

Comment

In these experiments, the teratogenic effects following injection of mice with vitamin A on the 8th to 13th days of pregnancy were more intense the earlier the agent was administered. In group A treated on the eighth day of pregnancy, the incidence of embryonic deaths was 92%, and all surviving fetuses presented malformations. In the ddN strain of mice which were used in a pilot test, all embryos died following treatment on the eighth day. The incidence of malformations was reduced, but only gradually, in mice treated at later stages of pregnancy, and over 21% malformed fetuses were still observable in group F treated on the 13th day. The effects of the agent were extensive, therefore, for at least five or six days.

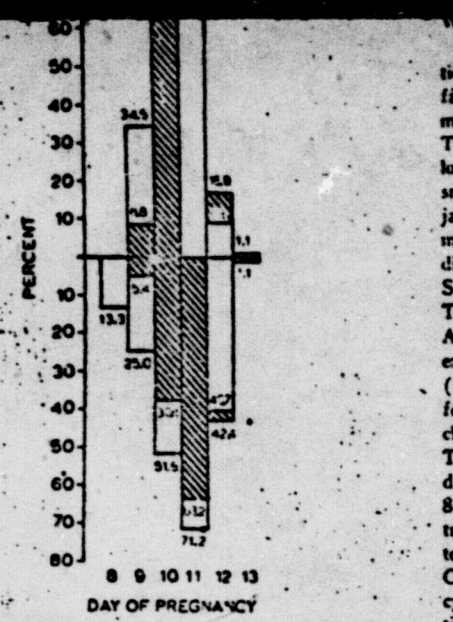

Fig 6.—Rates of malformations of the limbs and digits by day of pregnancy on which vitamin A was administered.

Exencephalia in rats was not a frequent manifestation after administration of vitamin A as shown in papers by Giroud and Martinet (1956),[7] Woollam and Millen (1957),[20] and Araki (1958).[1] Spina bifida aperta was rarely induced in mice when they were treated with another kind of agent. However, some cases of spina bifida were manifested in the present experiments with hypervitaminosis-A.

There were some characteristic malformations observed. One example was the craniofacial-pattern microcephalia associated with malformations of the jaw, mouth and auricle. The principal features of the defect were as follows; foreshortening of the frontal region and snout with incomplete formation of the lower jaw, and variously micrognathia, agnathia, microstomia, anostomia, anotia and absence, dislocation, or malformation of the auricle. Such fetuses presented a strange appearance. The internal ear was also abnormally formed. A similarly induced abnormality of the internal ear of the rat has been studied by Nakamura (1958)[23] in detail. To all appearances, these fetuses with the above malformations could be classified as otocephalia and its allied conditions. Treatment on the ninth day of gestation produced the highest frequency of the defects—81.75%. The next highest frequency followed treatment on the eighth day—80%. After the tenth day, the incidence was markedly reduced. Otocephalia has a close relationship to the cyclopia-arrhinencephalia group of malformations in morphogenesis. When pregnant mice were exposed to x-radiation on the ninth day of pregnancy, malformations belonging to the cyclopia-arrhinencephalia group, especially arrhinencephalias, were manifested in considerable numbers (Murakami et al, 1962).[17] Thus, a coincidence is seen in the period critical for arrhinencephalia caused by x-radiation, and the above malformations with their characteristic craniofacial pattern due to hypervitaminosis A. However, in the above fetuses with craniofacial patterns, the auricle did not show a coincidental location when compared with real otocephalia in animals or human beings. Furthermore, in experiments employing the rabbit, the auricle was neither lost nor dislocated (Murakami, 1964).[22] Therefore, in the specially complicated malformations with craniofacial pattern there is no definite evidence to classify them with otocephalia or its allied conditions. Deusible et al (1959)[4] called the condition an anomalous oculodentofacial pattern, and later Kaiser (1960)[10] also analyzed the condition in detail.

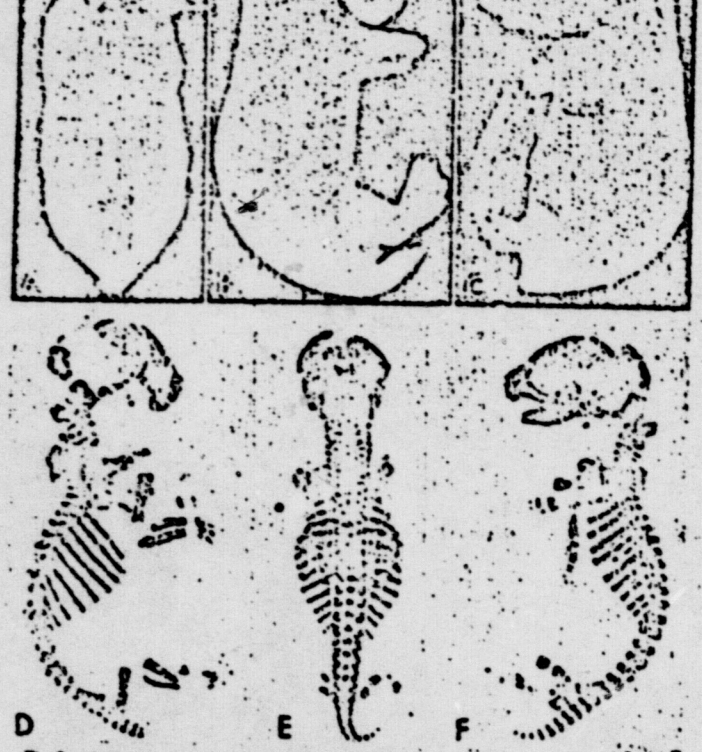

Fig 7—*A*, abnormal fetus with exencephalia, anostomia, exophthalmus, spina bifida aperta, and taillessness after intraperitoneal injection of the mother with 15,000 IU vitamin A on the eighth day of pregnancy.

B, abnormal fetus with microcephalia, agnathia, anotia, exophthalmus, open eye, brachydactylism and short-tailedness after intraperitoneal injection of the mother with 15,000 IU vitamin A on the eighth day of pregnancy.

C, abnormal fetus with micromelia after similar treatment on the 11th day of pregnancy. This fetus also had micrognathia and cleft palate.

D, skeleton of an abnormal fetus with similar cranio-facial pattern shown in B after similar treatment on the ninth day of pregnancy. The shape of the cranial bone, especially the frontal, temporal, and premaxillar bones are abnormal. A rudimental mandibular bone is fused with the maxilla.

E, skeleton of an abnormal fetus with malformed vertebrae and ribs after similar treatment on the tenth day of pregnancy. Rami of the posterior arch of the cervical vertebrae are involved in fragmentations and the rib has buds. Bones forming the limb-girdle and limbs are also involved in deformity.

F, skeleton of an abnormal fetus with micromelia after similar treatment on the 11th day of pregnancy. Long bones of the extremity are involved in malformation: ossification of the humerus and femur is absent. Bones of the forearm and lower leg are also malformed.

present paper. Such exophthalmoses could not be produced in rabbit fetuses by hypervitaminosis-A of the mother during pregnancy (Murakami, 1964).[22]

There were no cases of harelip, although the incidence of cleft palate was high particularly in mice treated with vitamin A on the 11th day of pregnancy. However, in contrast to the results with x-radiation, the manifestation of cleft palate did not present two phasic elevations of incidence. Giroud et al and Kalter et al succeeded in getting cleft palates by oral administration of vitamin A, whereas in experiments employing subcutaneous injection of the agent done by Wollam et al (1957),[26] cleft palate was not detected. Takekoshi (1961)[24,25] produced cleft palate by intramuscular injection. The high incidence of the defect seen by the authors of the present paper may be due to the amount of the agent used and the route of administration.

Anal atresia was another of the characteristic malformations caused by hypervitaminosis-A. Kalter et al have also described this pattern of defect, although the critical stage seemed to be a day later. Such differences in the critical stage may be caused by differences in progression of development between the strains of mice or by differences in the timing of treatment. Malformations of the tail were manifested chiefly in groups treated on the eighth, ninth, and tenth days, and the earlier the time of administration the higher the frequency. Kalter et al[11] also stated that malformations of the tail were manifested following treatment at 8½ and 9½ days of pregnancy, which corresponds roughly to the 9th and 10th day of pregnancy in the present experiment.

Malformations of the extremities were frequently seen. Most of the defects were typical micromelias such as what are sometimes called phocomelias. These were seen especially in the forelimbs of mice treated from the 10th to 11th day, and in the hindlimbs of mice treated on the 11th day. Reduction in number of digits was associated with micromelia. The difference in incidence of malformations of the extremities

Giroud et al and Kalter et al. Similar findings were shown both in experiments of the present paper and those of Kalter and Warkany.[11] Millen (1962)[14] injected the agent subcutaneously in the rat and produced meromelus syndactylus and amelias in about 43% of fetuses. No such cases were found in experiments by the present authors. It is hard to compare results of experiments done by different investigators because species and strains of animals used, as well as amount of the agent and route of its administration, may be different. However, the kind of malformations produced have been similar. In the present experiment, many micromelias were produced. Long bones of the extremities presented specific involvement and the degree of the micromelia was high, but no synostosis in bones of the forelimb as seen following x-radiation was detected. Also, ectrodactylism was manifested in the forelimb of fetuses treated on the 10th and 11th day, but it was manifested in the hindlimb in groups of the 10th, 11th and 12th day. With x-radiation, ectrodactylism was detected chiefly in the forelimb in the group treated on the 12th day of pregnancy (Murakami et al, 1963).[20] While administration of hypervitaminosis-A caused exencephalias and spina bifida aperta, hypervitaminosis-A during early stages of pregnancy seemed to have destructive effects directly upon the primordial retina. Therefore, further development of the eye was not disturbed as in experiments with x-radiations. Hypervitaminosis-A exerts a serious effect upon formation of bones of the face. Formation of the snout, mandible, and the temporal bone, especially the zygomatic arch, were involved in the disturbance. Many cleft palates were also manifested. Presumably, the agent affected the primordium of the palate, ie, the maxillary arch itself, thus disturbing further development. This agent does not seem to interfere with formation of the tail after the primordium is formed. The limb-bud, and hand or foot plate, seem to be susceptible to hypervitaminosis-A. Therefore, hypervitaminosis-A exerts a suppressive effect chiefly upon mesenchymal tissue just before its differentiation into the primordium, or on mesenchymal

investigators, ectodermal organs also seemed to be more susceptible than observed in the results of the present experiments. The cause may be explained when an investigator uses different species of animals and also different ways of treating the animals.

In our experiments, marked rises in the frequency manifestation of specific malformations ranged over a period of two to three days, whereas, with x-radiation, such rises are usually limited to only one day. This point may be due to the fact that x-radiation affects embryos for relatively short times and only in the radiosensitive stage of development. However, with hypervitaminosis-A, injected intraperitoneally, the teratogenic effect apparently undergues a gradual decrease until a certain level is reached.

There were characteristic changes in the skeletal system. Those changes were marked in the craniofacial region, vertebrae, and extremities.

In hypervitaminosis-A, the time range of the critical period for each malformation seemed to be a little longer than in experiments with x-radiation. This may be due to the nature of the agent and the continued effect it exerts until a certain level is reached.

Generally, in these experiments, involvement of mesenchymal tissue was prominent.

Summary

Pregnant (CF_1 strain) mice were divided into six groups from the 8th to 13th day of pregnancy. Each group was administered a single dose of 15,000 IU vitamin A water miscible solution intraperitoneally, and the fetuses were examined for gross malformations and skeletal changes. Some fetuses were also studied in histologic sections.

Many characteristic malformations were manifested according to the stage of pregnancy at which the agent was administered. Exencephalias were detected in groups treated on the eighth or ninth day. Spina bifida aperta was found following treatment on the 8th, 10th and 11th days of pregnancy. Complicated malformations with craniofacial patterns such as microcephalia, reduction malformations of the jaw, mouth, and auricle in various degrees were seen in groups treated on the eighth and ninth days. In overall appearance, these defects seem to have some resemblance to otocephalias, but there was no evidence conclusive enough to classify them as otocephalias. Many cleft palates were produced by treatment on the 10th day; next in line were groups treated on the 9th and 11th days. In groups treated on the 10th and 11th day, many fetuses with micromelia showing a typical phocomelia were detected. In many of those cases, ectrodactylism was an associated

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Of course, it can hardly be said that we treat pregnancy as an illness. We have just lived through a difficult decade during which pregnancy and delivery have been practiced exclusively as a time of sweetness and light. America's greatest concern has not been with the welfare of the child, but with whether or not the husband would be allowed in the delivery room. That the birth of a child is a family milestone no one would deny, but it must be remembered that the event has far more than sentimental significance.—A. C. Barnes, The Hazards of Being Born, *The Johns Hopkins Magazine* 15:10 (Oct) 1963.

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NUTRITION

SEVENTH EDITION

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The carotenes and vitamin A go through preparation stages for use in the body. In the human being the intestinal wall is the main site of conversion of carotene into vitamin A, with some also occurring in the liver. An enzyme system, possibly carotenase, breaks down the hydrocarbon into simpler molecules, forming first vitamin A aldehyde and then the free or alcohol form. Fats and bile salts must be present in order for carotene to be absorbed. Man does not seem to be able to convert carotene as efficiently as does the rat.

Vitamin A is absorbed from the upper part of the intestinal tract. If vitamin A ester is ingested in an oily medium such as cod liver oil, it has to be saponified before it can be absorbed. If the ester is finely emulsified or is in an aqueous dispersion, saponification is not necessary. Bile salts are required for efficient absorption of vitamin A as well as carotene. The ester is hydrolyzed into the alcohol before passage through the intestinal wall. In the cellular mucosa it is again esterified and appears in the lymph largely as vitamin A palmitate. The blood stream then carries the vitamin to the liver where it may be stored in ester form. The liver can change the ester into vitamin A acid; in this form it is not stored but is rapidly oxidized. However, the acid can not be changed back into the aldehyde or the alcohol. When needed by the body, the ester stored in the liver is hydrolyzed into vitamin A alcohol or acid which is carried then by the blood to the parts that need it.

The functions of vitamin A

Vitamin A aldehyde performs specific metabolic roles. The function that vitamin A plays in vision is comparatively well understood. In the retina of the eye are two kinds of light receptors. The cones in the center of the retina contain the pigment iodopsin or visual violet and are associated with bright light or photopic vision. Rods as well as cones are in the remainder of the retina, the proportion of the rods increasing as the periphery is reached. The photoreceptor substance in the rods is called rhodopsin or visual purple and is associated with scotopic or dim light vision. Brown and Wald have shown that 11-cis retinal is the specific aldehyde which combines with opsin in the human eye to form rhodopsin. The pigment breaks down in the presence of light and is rebuilt in the dark. Some vitamin A is used up in the reaction and, therefore, unless there is a sufficient supply in the diet or in the body, rod vision is impaired and night blindness results. By means of measurements it is possible to determine a person's light threshold and this in turn may be related to vitamin A metabolism.

The aldehyde form of the vitamin also plays a role in reproductive processes. It has been found that neither sex of the rat reproduces normally unless vitamin A is contained in the diet, either as the aldehyde or an "active form" of the vitamin derived from it. This is evidenced by cessation of

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spermatogenesis in the male and by fetal resorption in the female rat. The biochemical reaction involved here is not known.

Optimal storage of vitamin A in the liver is important since normal development of fetal tissue may be affected adversely by a prenatal diet low in the factor. When the food of pregnant rats was deficient in vitamin A, Warkany and co-workers found that the young at birth had congenital malformations; these defects occurred in both skeletal and soft tissues. Parts frequently affected included the tibia, mandible, ribs, eyes, and cardiovascular system. It has also been shown that the offspring of cows fed a diet low in vitamin A developed eye abnormalities and paralysis.

However, it is known that man has a comparatively short organogenetic period, the time when most malformations are determined. The first trimester of pregnancy in the human being is considered the critical period and lack of vitamin A during this time may cause miscarriage. A specific relationship between dietary lack and congenital malformations in human beings has not been demonstrated and, according to Warkany, is difficult to prove.

Vitamin A acid is essential in several biochemical reactions. Since retinoic acid is rapidly metabolized in the body and cannot be changed to the aldehyde form, it will not prevent the occurrence of night blindness and reproductive failure. However, as Dowling and Wald demonstrated in 1960, the acid form of the vitamin has potent vitamin A activity.

Wolf and co-workers have shown that vitamin A acid can synthesize mucopolysaccharides; it is thought that the factor causes the release of a proteolytic enzyme from intracellular particles called lysosomes, which are similar in size to mitochondria. This stimulates the secretion of mucus by the epithelia. Lining the tracts and organs of the body are epithelial cells which serve to protect and keep healthy the various parts. Studies made on the eyes, certain glands, the respiratory and genitourinary tracts indicate that when vitamin A is lacking these cells are changed in form, becoming stratified and keratinized, and the cilia normally present in the tracts are lost.

In the young of a species the eyes may be the first part of the body to be affected by a lack of vitamin A. Biomicroscopic examination will show ocular lesions, a condition known as xerosis conjunctivae. This is the early stage of a condition which is later recognized as xerophthalmia (Figure 11-3).

In older animals the lungs are frequently affected. A correlation between the amount of vitamin A in the diet and the prevalence of tuberculosis has been noted in human beings. Sinus trouble and kidney and bladder disorders may also arise as a result of the abnormalities of the epithelium during avitaminosis A.*

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* The term "avitaminosis" is used to indicate a condition or state caused by the lack of a vitamin.

Teratogenicity

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Effect of Vitamin A Deficiency or Excess on the Oxidative Phosphorylation by Rat Liver Mitochondria*

(Received for publication, October 5, 1965)

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Rat

SUMMARY

Liver mitochondria from hypo- or hypervitaminotic-A rats exhibited low efficiency for coupled oxidative phosphorylation. Supplementation *in vitro* or *in vivo* with retinyl acetate, but not with retinoic acid, restored low phosphorus to oxygen ratios to normal.

Uncoupling of oxidative phosphorylation occurred with nicotinamide adenine dinucleotide-linked and non-NAD-linked substrates.

Serum albumin added to mitochondrial suspensions from livers of vitamin A-deficient or toxic rats restored normal oxidative phosphorylation efficiencies. Tri-o-cresyl phosphate caused uncoupling which was not restored by the addition of retinyl acetate.

An inherent instability of liver mitochondria from vitamin A-deficient and toxic rats is indicated because their endogenous oxidative phosphorylation is lower than that of mitochondria from normal animals. It is suggested that vitamin A is required in mitochondrial membranes at an optimum concentration; variations below or above this concentration cause these membranes to become unstable. Deviation from optimum may induce functional changes in enzymes associated with oxidative phosphorylation.

The gross symptoms produced by dietary deficiency or excess of vitamin A have been known for years, but the biochemical origin of the general morphological changes has not been traced to a particular area of intermediary metabolism. In previous reports (1, 2) we indicated that liver homogenates from rats suffering from dietary deficiency or excess of vitamin A showed an increased initial (30 min) respiration rate, followed by a drastic respiratory decline when succinate or α-ketoglutarate was the substrate. This pattern was essentially similar to the respiratory decline noted by Corwin and Schwarz (3) in livers from vitamin E-deficient rats. DeLuca *et al.* (4) had previously shown a significant increase in initial (30-min) oxygen uptake by liver homogenates from vitamin A-deficient rats when any of several Krebs cycle acids was used as substrate. Vignais (5) noted an increase in nicotinamide adenine dinucleotide phosphate cytochrome *c* reductase and a decrease in pyridine nucleotide transhydrogenase activities of liver mitochondria from vitamin A-deficient rats. He suggested that these changes might cause respiration to be uncoupled from phosphorylation and could account for any observed elevation in basal metabolic rates. Dingle and Lucy (6) showed that the molecular specificity for lysis of rabbit erythrocytes by compounds in the vitamin A series is similar to that for the prevention of vitamin A deficiency. These authors hypothesized that the site of action of vitamin A is at the lipoprotein membrane of cells and their organelles and that the role of the vitamin might be to control permeability. Dingle *et al.* (7, 8) reported that alterations in metabolism which occur in the presence of excess vitamin A may be associated with the swelling action of the vitamin on mitochondria. Wolf *et al.* (9), on the basis of a preliminary experiment, concluded that there was no change in oxidative phosphorylation efficiencies due to a vitamin A deficiency.

The reports in the literature on the involvement of vitamin A in respiratory systems in general and oxidative phosphorylation in particular are limited and inconsistent. As a result, we undertook a study of phosphate esterification in respiring liver mitochondria associated with a deficiency or excess of vitamin A. This paper reports information which bears on the possible role of vitamin A in respiratory systems in controlling the permeability of mitochondrial membranes and thereby determining oxidative phosphorylation efficiencies. A comparison has been made of the effects of retinyl acetate and retinoic acid *in vivo* and *in vitro* on the maintenance and restoration of maximum P:O values in mitochondria. Some preliminary experiments are reported on the effect of bovine serum albumin on P:O ratios of liver mitochondria. The effect of tri-o-cresyl phosphate on the phosphorylating mechanism was studied because of previous reports (2, 10) on the action of this chemical in lowering liver vitamin A.

EXPERIMENTAL PROCEDURE

Materials—Nicotinamide adenine dinucleotide, ADP, ATP, and hexokinase (type III) were purchased from Sigma. Tri-o-cresyl phosphate, retinyl acetate, and retinoic acid were bought from Distillation Products. All of our more commonly used chemicals were of reagent grade and of the highest possible

* A preliminary report on part of this material was given at the 49th Federation of American Societies for Experimental Biology Convention at Atlantic City, New Jersey, April, 1965.

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TABLE I

Effect of vitamin A deficiency on oxidation of substrate by liver mitochondria in absence of phosphate acceptor system

The experimental details are described in the text. The results are expressed as microliters of O_2 consumed per 1 hour per mg of mitochondria nitrogen. The values represent the average of 3 or more rats per group per substrate.

Substrate	Rate of oxidation		Increase caused by deficiency
	Control rats*	Vitamin A-deficient rats	
			%
Succinate	31	50	74
β-Hydroxybutyrate	13	25	92
α-Ketoglutarate	24	33	37

* Rats in this group were fed vitamin A at a concentration of 5 mg per Kg of diet.

purity. Male weanling rats, purchased from Holtzman and weighing 45 to 50 g, were used in our studies.

Methods—All diets fed have been reported elsewhere (2). The animals were housed individually in raised wire bottom cages at a constant room temperature of 23 ± 2°. Diets and tap water were available *ad libitum*. Weight gain records were taken weekly until the growth curve of the rats in the vitamin A-deficient group began to flatten. Some of the rats in this group were sacrificed at this stage and termed mildly deficient. Weight gains for rats not sacrificed at this time were recorded daily thereafter until the deficient group began to show marked losses in weight. These animals were sacrificed at this stage and termed extremely deficient.

When the rats in the group on the control diet reached a weight of about 170 g, 15 of them were put on a high vitamin A regimen. They were given 17 mg (50,000 i.u.) of retinyl acetate orally by calibrated dropper per day for 5 days and weighed daily. Rats showing no loss in weight or signs of morbidity after two doses of vitamin A were sacrificed at this time and termed mildly toxic. Rats in this high vitamin A group dosed for the complete 5-day period consistently showed losses in weight. They were termed extremely toxic and sacrificed.

Rat liver mitochondria were prepared from a 10% (*w/v*) homogenate in a medium of 0.25 M deionized sucrose containing 0.002 M EDTA (Versene), according to the centrifugation method of Schneider (11). Versene was omitted from the final mitochondria suspension. The twice-washed mitochondria were resuspended in a volume of 0.25 M deionized sucrose such that each milliliter represented the mitochondria obtained from 1 g (wet weight) of tissue, with an average nitrogen content, determined by the micro-Kjeldahl technique, of 1.8 mg per ml. Prior to the preparation of the mitochondria, all additions of substances *in vitro* were made to the homogenates in a 1:2 ethanol-propylene glycol mixture and rehomogenized for 30 sec.

The system used for the assay of oxidative phosphorylation contained (with individual variations as indicated in the legends) 50 μmoles of phosphate buffer (pH 7.4), 40 μmoles of Tris, 4 μmoles of $MgCl_2$, 50 μmoles of glucose, 14 μmoles of NaF, 30 μmoles of substrate, 3 μmoles of ADP, 3 μmoles of NAD (when used), 3 μmoles of ATP, and 0.5 mg of hexokinase in a total volume of 3 ml, including 1 ml of mitochondria equivalent to about 1.8 mg of nitrogen suspended in 0.25 M deionized sucrose. The system was incubated at 37° with air as the gas phase for a period of 20 min, following a 5 min equilibration period. The center well contained 0.2 ml of 30% KOH absorbed on filter paper. Following an equilibration period of 5 min in the Warburg bath, the manometers were closed, and the zero time flasks were removed for inorganic phosphorus analysis. All zero time and experimental flasks were run in duplicate or triplicate. All runs included flasks for measuring the endogenous oxidative phosphorylation according to the method of Weinbach (12). The number of micromoles of phosphorus esterified was calculated as the difference in inorganic phosphorus between zero time and the corresponding samples incubated for 20 min. The figure was corrected for any endogenous oxidative phosphorylation and dephosphorylation of added ATP and ADP (13). Inorganic phosphorus was determined by the method of Lowry and Lόpez (14). The oxygen consumption for the incubated flasks and the P_i uptake values were used to calculate the P:O ratios. Nitrogen was determined on the original mitochondria suspension.

The comparison *in vitro* of the ability of retinyl acetate and retinoic acid to restore low P:O ratios to maximal values was determined on rats made vitamin A-deficient and subsequently repleted with either retinyl acetate or retinoic acid, at a concentration of 68 μg (200 i.u.) per day until they resumed normal growth, at which time they were sacrificed. For comparison, *in vitro*, these two compounds were added to the liver homogenate prior to the preparation of the mitochondria, at a concentration of 20 μg per ml. Additions of serum albumin were made *in vitro* in a similar manner at a concentration of 0.5 mg per ml of homogenate.

RESULTS

Vitamin A Deficiency—An impaired metabolic function was demonstrated in the mitochondrial fraction of the whole homogenate from vitamin A-deficient rats (Table I). In the absence of phosphate acceptor system (ADP, hexokinase, glucose), succinate, β hydroxybutyrate, and α ketoglutarate showed increased rates of oxidation of 74, 92, and 37%, respectively, compared to the controls. The apparent metabolic disturbance is corrected by addition of retinyl acetate *in vitro* (Table II).

Since the data in Table I show that the metabolic lesion seen in whole liver homogenates of vitamin A-deficient rats can be traced to a malfunction in the mitochondrial component, we began a detailed investigation of the oxidative phosphorylation efficiency of these mitochondria. Data in Table III summarize a typical experiment with respect to oxidative phosphorylation in the presence of three different substrates. With all three substrates, the mitochondria from mildly deficient rats showed a decreased efficiency in coupling phosphorylation to oxidation, compared to mitochondria from normally vitamin A-nurtured rats.

Effect of Hypervitaminosis A—As previously reported (2) excess vitamin A (17 mg per day) given to young adult male rats for 5 days caused a marked elevation in oxygen uptake by liver homogenates containing several added Krebs cycle acids. These results led us to investigate the effect of excess vitamin A on the ability of mitochondria from these rats to carry out coupled phosphorylation. A summary of these experiments is shown in Table III. With all substrates, phosphorus uptake is

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TABLE II

Comparison of retinyl acetate and retinoic acid on P:O ratios

Retinyl acetate or retinoic acid was fed to rats mildly deficient in vitamin A at 63 μg (210 I.U.) per day until the rats resumed normal growth for the studies *in vivo*. The additions were made *in vitro* to a 10% (w/v) liver homogenate from deficient rats at a concentration of 20 μg per ml prior to preparation of the mitochondria. Table III contains results for comparison of these values to comparable positive and negative (deficient) controls.

Substrate	No. of rats	P:O ratios			
		Retinyl acetate		Retinoic acid	
		In vivo	*In vitro*	*In vivo*	*In vitro*
Succinate	3	1.74 ± 0.08	1.65 ± 0.20	1.10 ± 0.05	1.20 ± 0.20
β-Hydroxybutyrate	3	2.91 ± 0.24	2.57 ± 0.15	1.60 ± 0.16	1.71 ± 0.28
α-Ketoglutarate	5	3.81 ± 0.25	3.60 ± 0.22	2.32 ± 0.27	2.25 ± 0.20

TABLE III

Effect of vitamin A deficiency and excess on oxidative phosphorylation

The experimental details are described in the text. The P:O ratios are recorded as the mean ± the standard error. The degree of deficiency or toxicity was determined as outlined in the text. Serum albumin was added to the 10% (w/v) homogenate prior to preparation of the mitochondria at a concentration of 0.5 mg per ml. The substrates, succinate, β-hydroxybutyrate, and α-ketoglutarate, were added to the Warburg vessel at a concentration of 30 μmoles in a total volume of 3 ml.

Substrate	No. of rats	Vitamin A status	ΔO₂	ΔPi	P:O ratio
			μatoms/mg N	μmoles/mg N	
Succinate	7	Normal	4.54	8.51	1.88 ± 0.11
Succinate	6	Mildly deficient	3.91	5.49	1.40 ± 0.14
Succinate	6	Extremely deficient	5.01	4.67	0.93 ± 0.12
Succinate	3	Mildly toxic	4.01	4.83	1.20 ± 0.05
β-Hydroxybutyrate	7	Normal	2.58	7.93	3.06 ± 0.29
β-Hydroxybutyrate	4	Mildly deficient	4.20	6.62	1.58 ± 0.20
β-Hydroxybutyrate	4	Mildly toxic	1.97	3.56	1.82 ± 0.19
β-Hydroxybutyrate	3	Extremely toxic	2.52	2.01	0.80 ± 0.06
β-Hydroxybutyrate	4	Mildly deficient + serum albumin	2.90	8.43	2.91 ± 0.15
β-Hydroxybutyrate	3	Mildly toxic + serum albumin	1.96	5.53	2.82 ± 0.05
α-Ketoglutarate	7	Normal	2.25	7.06	3.51 ± 0.15
α-Ketoglutarate	5	Mildly deficient	2.79	6.97	2.50 ± 0.02
α-Ketoglutarate	6	Mildly toxic	2.19	5.43	2.48 ± 0.28

decreased, resulting in a lowering of P:O ratios in mitochondria from the mildly toxic animals compared to the controls.

Effect of Severity of Vitamin A Deficiency or Toxicity.—Since the defects observed in the oxidative phosphorylation mechanism could be the result of a general debility of the rats in a state of severe deficiency or toxicity, we ran experiments with mildly deficient and mildly toxic rats along with those suffering from severe deficiency or toxicity. As seen from the data in Table III, the loss in ability of the mitochondria from the mildly deficient or toxic rats to carry out normal oxidative phosphorylation occurs quite early, and the severity of the deficiency or excess tends only to accentuate this defect. The decreased P:O ratios caused by a mild toxicity occur with both non-NAD-linked substrate (succinate) and NAD-linked substrates (α-ketoglutarate, β-hydroxybutyrate).

Effect of Bovine Serum Albumin.—Serum albumin has been shown to maintain and/or restore to normal otherwise impaired oxidative phosphorylation efficiencies (15, 16). Oxidative

TABLE IV

Effect of tri-o-cresyl phosphate on oxidative phosphorylation with succinate as substrate

Experimental conditions are described in the text. When fed, retinyl acetate was added at 5 mg per Kg of diet and tri-o-cresyl phosphate at 0.1%. Means ± standard errors of P:O ratios are for 5 rats per group.

Dietary supplement	No. of rats	ΔO₂	ΔPi	P:O ratio
		μatoms/mg N	μmoles/mg N	
Retinyl acetate	5	4.49	8.92	1.99 ± 0.09
Retinyl acetate + tri-o-cresyl phosphate	5	2.98	3.26	1.09 ± 0.06
None*	5	4.10	5.50	1.33 ± 0.16
Tri-o-cresyl phosphate	5	3.70	4.61	1.25 ± 0.05

* Vitamin A-deficient.

phosphorylation ratios in Table III illustrate the effectiveness of serum albumin in restoring low P:O ratios to maximum values, whether the adversely affected P:O ratios were due to a vitamin A deficiency or toxicity, when β hydroxybutyrate is the substrate.

Comparison of Retinyl Acetate and Retinoic Acid—A comparative study of these two substances of the vitamin A series in our vitamin A-deficient system is summarized in Table II. It is apparent from the results that retinoic acid is not effective, either *in vivo* or *in vitro*, in preventing or restoring low P:O ratios. On the other hand, retinyl acetate is completely effective.

Effect of Tri-o-cresyl Phosphate—We can see from the data of Table IV that tri-o-cresyl phosphate is a relatively effective uncoupler of oxidative phosphorylation when fed in the diet at 0.1%. When compared to the positive (retinyl acetate) and negative nonsupplemented controls, tri-o-cresyl phosphate causes a lowering in both oxygen and phosphorus uptake. The effect of tri-o-cresyl phosphate in causing low P:O ratios with succinate as substrate is not reversed by the addition of retinyl acetate.

DISCUSSION

Our results offer evidence that the capacity for maximum oxidative phosphorylation is severely impaired in mitochondria from vitamin A-deficient or toxic rats. The fact that uncoupling occurred with NAD-linked and non-NAD-linked substrates, in both mild and severe deficiency or toxicity, with little or no differences in ATPase activities of mitochondria from deficient (6.96 ± 0.2) and toxic (6.14 ± 0.8) rats on the one hand and from controls (6.83 ± 0.9) on the other, suggested that the results obtained are due to a true uncoupled oxidative phosphorylation, not an apparent uncoupling due to ATPase activity (expressed as micromoles of P per mg of N_2 per 20 min). The nature of the uncoupling effect is consistent with a general membrane disturbance and agrees with our previous observations (2) and those of DeLuca *et al.* (4) concerning the increased metabolic rates in vitamin A deficiency and toxicity.

Our findings are in contrast to those of Wolf *et al.* (9), who concluded that the depression of oxidative phosphorylation in vitamin A deficiency was not statistically significant. However, our studies were made on liver mitochondria and those of Wolf *et al.* were carried out on heart mitochondria. Lucy, Luscombe, and Dingle (8) have shown that high dosages of vitamin A are less effective in causing swelling in mitochondria from heart, spleen, and brain than from liver and kidney. There is evidence to support the fact that vitamin A deficiency or toxicity leads to mitochondrial swelling (17) as a result of changes in structure or function or both.

Several investigators have shown serum albumin added *in vitro* to be effective in the restoration of oxidative phosphorylation (15, 16). They have attributed this to at least three different effects: (*a*) the prevention of mitochondrial swelling, (*b*) removal of uncoupler through chelating action, and (*c*) an effect exerted by the free sulfhydryl group of albumin protein. Albumin has been shown to be effective in restoring normal oxidative phosphorylation in both vitamin A deficiency and toxicity; this could be due to any or all of the three functions postulated for the albumin effect. Possibly tri-o-cresyl phosphate causes uncoupling by interacting with the mitochondria at some unknown site, in a manner similar to certain uncoupling phenols (18). The apparent action of tri-o-cresyl phosphate is to lower the P:O ratio in normal but not in deficient rats.

Retinoic acid supports growth as well as retinyl acetate. It has been shown to be equal to vitamin A (19) in reducing cerebrospinal fluid pressure. On the other hand, retinoic acid does not maintain normal reproductive performance in male and female rats (20), does not maintain normal embryonic development in the chick (21), and does not replace retinol in the visual cycle (22). The ineffectiveness of retinoic acid in our system may be related in some way to its inability to function in these other biological roles.

Another aspect of these studies is the relation of vitamin A deficiency or excess to endogenous oxidative phosphorylation. In most cases endogenous oxidative phosphorylation was higher in the mitochondria from control rats than in that from deficient or toxic animals. This fact is important in the light of a study of endogenous oxidative phosphorylation by Weinbach, Sheffield, and Garbus (15), in which they concluded that the capacity for endogenous phosphorylation is related to the inherent stability of the mitochondria.

These results illustrate that vitamin A deficiency or excess has a profound effect on oxidative phosphorylation and that this effect can be explained by changes in mitochondrial membrane permeability.

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1276 *Pathology*

THE ETIOLOGY OF LIVER NECROSIS FOLLOWING ADMINISTRATION OF PROGESTERONE LATE IN PREGNANCY. John W. Craig, Boston Hosp. for Women, Harvard Med. Sch., Boston, Mass.

Lymphocidia (J.Nat.Can.Inst. 12:711, 1945) and Stanley, (Fed.Proc. 20:408, 1961), have suggested the presence of a toxemic like state following large doses of progesterone late in pregnancy in the rat. We have given progesterone (10 mg./day in olive oil) subcutaneously beginning at 15 days of gestation for 5 days in one series of 25 and continuing till sacrifice at 21-26 days of gestation in another series of 31 rats. The animals were sacrificed in groups at 21-26 days of gestation. As gestation was prolonged, the incidence of fetal intrauterine death increased. Concomitantly the incidence of myocarditis, endocarditis, extensive liver necrosis and interstitial pyelonephritis of the mother increased. The placentae showed early, degenerative changes in the labyrinth, then increasing evidence of chorionitis, labyrinthitis, necrosis and massive bacterial growth. In only one mother was renal cortical necrosis found. These changes in the uterus and those elsewhere in the body are consistent with overwhelming sepsis due to invasion from the massive bacterial growth in the uterus associated with necrotic material in the uterus. (Aided by Grant HD 01172, USPHS.)

1277 *Physiology*

IUD-INDUCED EMBRYONIC MORTALITY IN RABBITS. W. R. Dayton*, W. L. Williams* and W. F. Peterson, Dept. of Biochem., Univ. of Ga., Athens.

Two distinct effects of an intrauterine device in the rabbit occur: a) a localized effect in the IUD-containing uterine horn which results in a 38.4% reduction in the rate of implantation, and 2) a general effect, apparent in the second half of pregnancy which results in a high incidence of embryonic death. IUD's do not effect ovulation, sperm capacitation or fertilization. The anti-implantation effect may be related to an upset in carbohydrate metabolism based on a) a 38% decrease in total carbohydrate in uterine fluid from IUD-containing horns and a day blastocyst fluid, b) an increase in the free-sugar content of uterine fluid from IUD-containing horns and c) hypertonic glucose solutions inhibit implantation in uterine horns containing IUD's but not in control uterine horns. The IUD in rabbits offers a unique research tool for studies of implantation and embryonic death. This work supported by NIH Biomedical Grant 23068 and Training Grant No. 5 T01-HD-00140.

1278 *Physiology*

TERATOGENICITY OF VITAMIN A IN THE CANINE. Donald O. Wiesner* and Melvin J. Swenson, Department of Physiology & Pharmacology, College of Veterinary Medicine, Iowa State University, Ames, Iowa.

Vitamin A was given to mated Beagle bitches to determine the existence of a teratogenic effect. Daily oral administration of vitamin A in doses of 50,000 to 125,000 IU/Kg. of body weight and at varying periods from day 9 through day 31 of pregnancy was used. Whelping occurred normally or cesarean section was performed when signs of parturition were evident. Cleft palate was produced when daily treatment with 125,000 IU of vitamin A/Kg. included day 17 through day 22. Other abnormalities observed were deformed and accessory auricles, bisected testis, retarded litter size, failure to litter, unidentified fetuses and unusual pregnancy. (Supported in part by USPHS General Research Support Grant)

1279 *Pharmacology*

ANTIZYGOTIC ACTIVITY OF 2-METHYL-3-ETHYL-4-PHENYL-6-CYCLOHEXENE CARBOXYLIC ACID IN THE RAT. R. Rizzo and R. Hertz (spon: T. C. Smith), Ortho Research Foundation, Raritan, New Jersey.

2-methyl-3-ethyl-4-phenyl-6-cyclohexene carboxylic acid (ORF-3858) inhibited pregnancy in the rat when orally administered as a single dose of 25 mg./kg. on either of the first two days of gestation or when 10 mg./kg. was given on each of these days. Post-coital tubal flushings revealed that the drug caused lysis of the blastocysts as early as 60 hours but always by 84 hours after ovulation. The drug exhibited 2.36 times the oral antiprogestic potency of subcutaneous progesterone as assessed in the rat uterine weight test. Ethynyl estradiol, however, failed to duplicate the antizygotic effect of ORF-3858 even at dose levels as high as 500 mg./kg. ORF-3858 neither interfered with implantation nor acted as a progesterone antagonist but appeared to affect zygotes directly or by means of some alteration in tubal environment.

1280 *Biochemistry*

DECAPACITATION FACTOR, A NATURALLY-OCCURRING ANTIFERTILITY SUBSTANCE. H.G. Pinedo*, H.P. Chernoff*, T.O. Ahnoff, E.B. Fech and W.L. Williams, Biochem. Dept., Univ. of Ga., Athens.

Decapacitation factor (DF), a substance normally present in circulated sperm and in the seminal plasmas (SP) of several animal species, prevents sperm from fertilizing ova. It is removed from sperm, a process called capacitation, only by incubation in the uterus for several hours after which time sperm can fertilize ova. Using inhibition of the capacity of sperm to fertilize ova in the rabbit oviduct as an assay, DF was purified and some properties studied. Ultracentrifugation of bull and rabbit SP revealed a species difference in behavior of DF activity. After repeated ultracentrifugation and washing of the initially active pellet, DF activity remained entirely in the rabbit SP pellet but was completely removed from the bull SP pellet being recoverable in water washings. After proteolysis of the rabbit pellet, DF activity no longer sedimented. Gel filtration indicated a low molecular weight on the order of 500 for bull DF. Preliminary experiments suggest that DF is extractable from aqueous solution by chloroform-methanol. Direct injection of purified DF into the rabbit uterus followed by natural mating markedly lowered the number of ova subsequently fertilized suggesting a possible contraceptive approach. Supported by NIH research grant GM-10034, training grant 1 T1-HD 140 and Cor. Dev. 2-63-483.

1281 *Physiology*

CRITICAL EXPOSURE TIME FOR ANDROGEN STERILIZATION OF THE FEMALE RAT. R. Gorski and I. Arai*, Dept. of Anatomy and Brain Res. Inst., UCLA Sch. Med., Los Angeles, Calif.

Testosterone propionate (TP) induces anovulatory sterility when given to 5 day old females. Thirty µg TP resulted in a sterility incidence (SI, percent animals anovulatory in groups of at least 10) of 92 at 45 days and 100 at 90 days of age. This effect of 30 µg TP was prevented by 43 mg/rat pentobarbital (PB) given with the TP and again 4 hours later: SI only 7 at 45 days, and 14 at 90 days of age. This preventive action of two injections of PB was inhibited by simultaneous injections of Metrazol (M; 2 mg/rat). An SI of 73 and 70 was observed 45 and 90 days following the injection of TP, PB, and M. The minimal neonatal exposure to TP needed for sterility was studied by injecting the two injections of PB at various intervals following TP treatment. Treatment with PB 1, 6, 12, or 24 hours after TP resulted in an SI of 34, 25, 7% and 0%, respectively. A single injection of phenobarbital (PB; 43 mg/rat) given 0, 1, 4, or 24 hours after TP produced an SI of 14, 54, 82, and 83, respectively. Although the nature of this protective effect seen on day 45 is unknown, two tentative conclusions are: Exposure during the first few hours after TP is critical since a dose of PB, ineffective after 3 hours, can block the effect of TP when given with it. A second phase in the inductive action of TP is PB sensitive and lasts about 12 hours.

Blood Coagulation II

1282

FIBRINOLYTIC AND ESTEROLYTIC AC PHATE FUGL)BULIN. P. Horjel* Med. Div., Bellevue Hosp., N.Y.

Human plasma euglobulin prepared wi creased fibrinolytic (Brakman and Astr acetyl lysine methyl esterase (ALMe)-Yale U., 1964) in comparison with o were undertaken to characterize the m to lose might its fibrinolytic activity, activity using arginine and lysine ester globulins, and has diminished 6-8 glob trophoresis as compared to E and plas not inhibited by soybean inhibitor or by plasma. Celite incubation studies show in MPE is not the result of contact acti 2 peaks (P1, P2) by Sephadex G-200 and contains lysine esterase and fibrin clot fractions and does not lyse plasminogen plasminogen. P1 esterase activity resu lysine Me/ALMe/TAMe:2/1/0.2. The activator and esterase have a M. Grant NB-03346-04, and Am. Cancer S

1283

CHANGES IN THE INTRINSIC SYSTEM DU TION. R. L. Bowers*, J. Blevins* a Mannering). Hematology Dept., Ms. and Med. Dept., Columbia Univ., New

Previous work demonstrated Porto activated by tissue thromboplastin exception to blood cells had by two studies were made to a patient with bacteroides who manifested a prolon Intravascular coagulation was indic and excessive fibrinolysis by elevated levels. Heparin corrected def During defibrination 1-stage factor higher than 2-stage levels. Similar several other patients with defibri ulability," and the presence of act is postulated. Comparison of coag defibrination and during a 1-year reduced Factor VIII (2-stage) level Factor V and XI levels and normal (1-stage) levels during defibrination. ciently higher during defibrinatio sibly resulted from activation of mechanism. (Supported by USPHS Gr AM13502-01 and Nat. Chapt. Research.

1284

ELEVATED FACTOR VIII (AHG) ACTIVI Robert L. Rosenthal and Esther G Diseases and Med. Center, New Yor

A previous finding of marked e in a patient with Acute Promyelocy R.L. Blood 21:649,1963) prompted VIII as well as factors IX and XI thromboplastin method and factor methods in 12 adults with Acute L myeloblastic, 1 monocytoid). Resul

	Controls		Patients		
	Mean (%)	Range	N	#	Range
F.VIII%	71	50-118	12	(12)	121
F.IX%	96	58-129	10	(10)	97
F.XI%	93	60-121	10	(10)	109
F.VII	95	80-110	0	(11)	96

*N denotes number of patients(s
Increased levels of factor VIII a 10 out of 12 patients, while only creased factor IX and XI activiti in 4 instances and decreased in 2 indicate a consistent, moderate e activity in patients with untreat Leukemia. (Supported by NIH Grant

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Nutrition of the embryo

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Laboratoire d'Histologie, Faculté de Médecine, Paris, France

Many factors concerning normal and abnormal development of the embryo have been thought of for a long time, but very few in correlation with its nutritional requirements. One allusion is given in the Bible: The fathers have eaten unripe grapes, and the teeth of the children are set on edge. According to Xenophon, women are usually badly nourished during pregnancy and they are obliged to weave. He writes: In these conditions it is not possible to delude ourselves on the future of the child.

In the more recent past, there was a widespread idea that good nutrition and good reproduction were related, but interest in values of foods was especially focused on their good effects on sexual stimulation. According to de Leron (19) the artichoke is able to incite the most timorous and spellbound to amorous dalliance. In the *Thesaurus Pauperum*, Peter the Spaniard claimed that the radish is very useful to the uterus and facilitates the expulsion of boys.

It was impossible in earlier times to go further because of the difficulties which existed. It was necessary to know the exact composition of foods and to use purified or completely synthetic diets in experiments, since almost all were dependent on withdrawal of definite substances.

Thus, it is only in modern times when the problem of nutrition of the adult and of the young is almost solved that the problem of the nutrition of the embryo is being seriously considered. In 1911, Hart et al. (127) showed in cows that immature and stillborn fetuses were the result of a diet poor in calcium. In 1935, Hale (126) demonstrated that malformations in piglets were the result of a maternal vitamin A deficiency, after having eliminated hereditary action, the hypothesis in favor at that time to explain malformations (Fig. 1).

Since then considerable work has been done concerning embryonic requirements, the influence of deficiencies and excesses, and the importance of an equilibrium; the correlation between nutritional and genetic conditions is more and more known.

ROLE OF FOODSTUFFS FOR BIRDS AND MAMMALIAN EMBRYOS

The feeding of the embryo is insured by the egg or by the mother during gestation. For many animals and especially birds the problem of embryo requirement is solved in advance, the female stocking the nutritional material in her eggs; thus its normal feeding is very important.

The yolk prepared in the ovary consists of proteins (phosphoprotein, ovovitellin and others, especially ovolivetin) and of lipids (neutral fats, phosphatides, and cholesterol), but few carbohydrates. Proteins and lipoproteins of the yolk and their variations during incubation have been the subject of recent investigations (1, 230, 272, 282). The yolk contains all vitamins except ascorbic acid. It also contains many inorganic constituents in various quantities. Only F, Ag, Cr, and Pb seem normally lacking. Albumen is added in the oviduct but it contains less nutrients than the yolk.

Naturally the value of the egg depends on the nutrition of the hen: Romanoff and Romanoff (263) claimed that egg production is closely dependent upon the quality of food. Some deficiencies and their repercussions must be presumed. Also, in accord with active fixation by the egg, some substances may be in excess, or other abnormal ones may be present such as selenium, boron, lead, and radioactive strontium.

The mammalian embryo takes its food from its mother. In the earliest stage, the ovum remains free in the fallopian tube and uterus which both contain proteins (197, 276). As a segmented egg, and as a blastocyst, it absorbs a few foodstuffs from the surrounding fluid (186). It grows very little and its development consists mainly in its subdivision into small cells; its requirements are almost limited to those of survival. When the ovum is on the uterine mucosa or implanted in it, it has an easy source of nutrition and develops rapidly.

In some species, the embryos utilize an embryotrophe, composed of a secretion of the uterine glands, the uterine milk (Ungulata), or damaged autolyzing cells, including blood cells (Carnivora): some special part of the chorion insures the respiratory function. In the placenta of many other mammals, humans included, there is more or less intimate connection between the embryonic vessels and the maternal blood. Thus the various nutrients and oxygen are provided simultaneously.

Naturally the value of the placental function is at first dependent on the nutrition of the mother herself. Its value increases with the mother's age and parity, and depends also on her size. Some crossings of various strains of different size (horses (302); sheep, by transfer of eggs (138, 139)) illustrate this fact.

From the Nutrition Symposium on "Nutrition and Prenatal Development" presented at the 51st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, Ill., May 11, 1945.

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In order to insure the increasing needs of the fetus during gestation, the maternal organism modifies its metabolism; it fixes more substances than usual, storing proteins, mineral salts, and other substances, in order to be able to insure the necessary transfer. Yet Zachanjewski (349) claimed a daily retention of 3–5 g nitrogen to the end of gestation in the woman. Macy and Hunscher (195), who made a series of continuous balances on pregnant women, demonstrate clearly the nitrogen storage and the cumulative reserves of Cl, P, Na, Ca, and Mg. In the rat, Rombauts et al. (264) showed that a considerable retention of nitrogen may occur. Compared with a period immediately preceding mating, the daily nitrogen retention was increased by 93 mg during the period 0–4 days and progressively by 131 mg during 16–20 days (Fig. 2). When the embryos are suppressed, the placenta remaining in situ, the weight of the mother continues to increase (315); the retention of nutrients is almost the same (32). Thus the storage by the mother depends on the placenta and, it seems, on its hormones (Fig. 3).

FIG. 1. Piglet with vitamin A deficiency. Note microphthalmy and abnormalities of the ear. (According to Hale (126).)

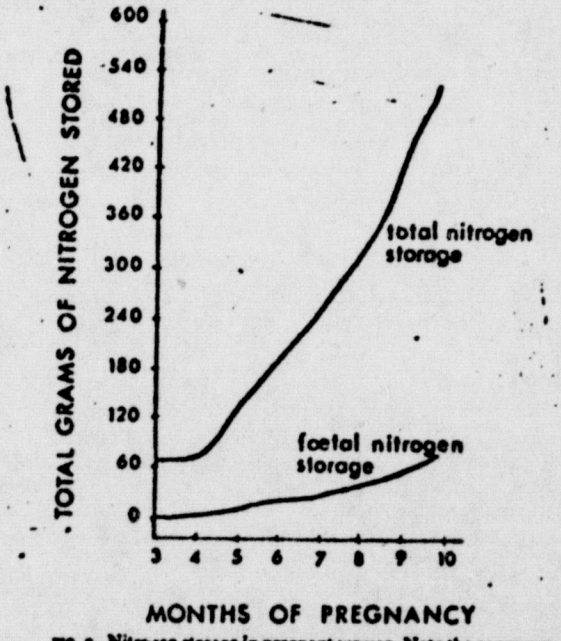

FIG. 2. Nitrogen storage in pregnant women. Note the enormous storage in the mother's body in comparison with the fixation in the embryo. (Modified from the data of Macy and Hunscher (195).)

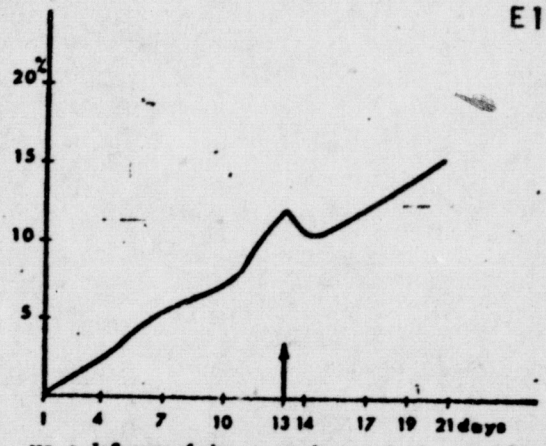

FIG. 3. Influence of placenta on the growth of pregnant rat when only the fetus is removed, the placenta remaining in the uterus (arrow). (Modified from data of Bourdel and Jacquot (32).)

The functional value of the placenta is of the first importance. Its size and its circulation are fundamental, as experiments of MacLaren and Michie (193), and Wiggelsworth (333) have demonstrated. It is also the same for its normal structure. Infants weighing less than 2.5 kg (premature) but born at term have been considered undernourished, and deficient function of the placenta was envisaged. Scott and Usher (277) do not emphasize the condition of the placenta, but many observations are significant; Gruenwald and Connell (124), Gershon and Strauss (100), Warkany et al. (325), and Bazsó and Gaál (21) have noted in these cases the exaggerated presence of avascular villi and infarctlike sequestration of large areas. Such defective conditions of the placenta could explain the delayed growth of the fetus.

UTILIZATION OF THE FOODSTUFFS

The foodstuffs are necessary to the embryo for building its tissues and organs and insuring the energy necessary to its life and especially to its synthetic processes. Carbohydrates are often utilized for energy, with lipids and even proteins as secondary sources. For synthesis, the basis of the growth of the embryo, the requirement for protein is naturally the most important. In accord with the modern view on the role of nucleic acids in protein synthesis, we must think of the successive production of deoxyribonucleines, ribonucleines, and then the various proteins.

According to the old morphological observations it

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was possible to foresee the necessity to build more and more numerous nuclei. Long ago Godlevski (114) and Loeb (182) observed in the sea urchin egg an unmistakable increase in total nuclear material during its development from fertilized egg to free swimming pluteus. On the same embryos, Brachet (34) confirmed the increase of DNA by chemical methods.

Deoxyribonucleic acid

	milligrams per gram dry weight
Fertilized eggs	0.1
Gastrulae	6.8
Plutei	13.6

After the deoxyribonucleines, the ribonucleoproteides must be synthesized since they serve as intermediates between the former and the new proteins. Winick and Noble (341) have studied such an evolution in the rat from 10 days after mating to maturity. Kafiani and Timofeeva (155) studying a fish embryo have noted that the synthesis of RNA, at first slow in the nuclei, increases rapidly. Thomson and Biggers (305), using actinomycin D or mitomycin which blocks RNA synthesis, stopped the segmentation of mouse eggs. In older embryos, Mori and Iso (215), utilizing ^{35}S-methionine in rabbits, noted that rate of protein synthesis seemed to parallel the RNA concentration. Analogous studies were done on birds by Sugimoto (291), Taussig (298), and Coffey et al. (57).

REQUIREMENTS IN CORRELATION WITH VARIOUS EMBRYONIC PHENOMENA

In the evolution of the embryo, three phenomena may be considered: maintenance, differentiation, and growth. Maintenance or survival may be easily separated, but it is not so evident for the distinction between differentiation and growth. During the process of differentiation, some growth is included corresponding to new structures, but after their appearance their increase essentially constitutes growth.

This distinction is important because the requirements of these phenomena are not the same. Spratt (288) studying cultures of chick embryos in defined media has demonstrated that the requirements for maintenance are very small, those for differentiation are greater, but those for growth are very important.

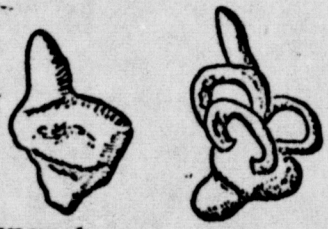

FIG. 4. Inner ears of a normal embryo (left) and of a deficient embryo (pantothenic acid deficiency) of the same size but older. Differentiation has progressed even though the growth is slowed. (According to Giroud (103).)

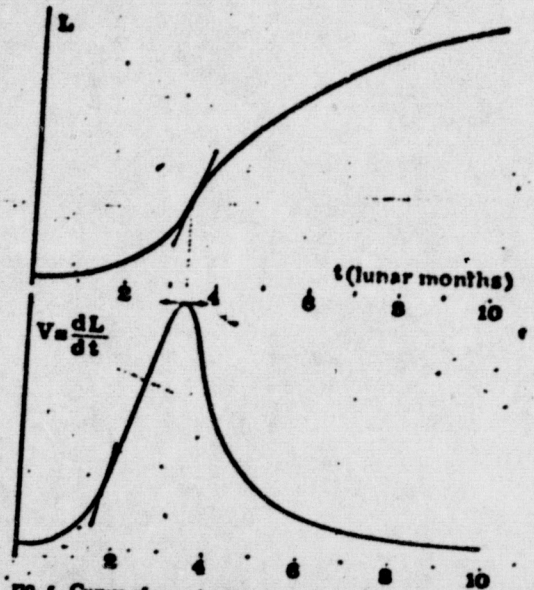

FIG. 5. Curves of growth of human embryo. On the top, curve of linear (natural) growth. It increases throughout the pregnancy. On the bottom, curve of rate of growth. After a sharp increase it decreases during the pregnancy. (According to Pineau (245).)

When we consider the evolution in vitro of isolated various anlage of chick embryo we see the same differences (284, 290, 331, 345). Wolff and colleagues (345) having adjusted a culture medium, established that sulfur-containing amino acids (cysteine or methionine) were generally essential for the maintenance of life and differentiation; that arginine, lysine, and glutamic acid, together or separately, were indispensable for differentiation; and that other amino acids and some vitamins were favorable to growth. These results show that, for a given organ, the requirements are different for its survival, differentiation, or growth. Singer and Cerecedo (284) have also noted that the required ratios of lysine, leucine, and tryptophan are not the same for maintenance and for growth.

It is the same for the mammalian embryo living in the uterus. The growth requirements are greater than those for differentiation. For example, in pantothenic acid deficiency the growth of the embryo is slowed, but if we compare one stunted embryo to a normal one of the same size but younger, it is easy to note that in the deficient embryo differentiation has nevertheless progressed. The fact is evident for the inner ear: its size is the same but the complete labyrinthine structures have appeared (103) (Fig. 4).

In humans, we observe the same facts. In the at-term newborns weighing less than 2.5 kg, growth was slowed but differentiation had nevertheless progressed. Today they are rightly labeled retarded or undernourished.

Growth of the embryo. Concerning growth two points of

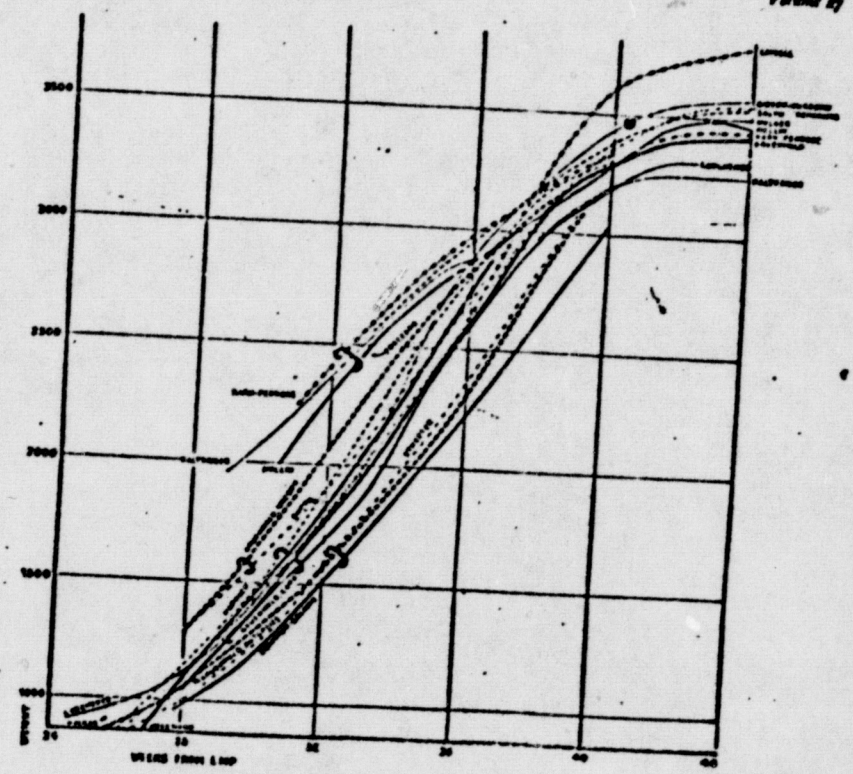

FIG. 6. Curve of weight of human embryo according to the weeks after last menstrual period. The inflection in the last 2 months reveals the insufficiency of the nutritional line (mother and placenta). (Courtesy of Gruenwald (123).)

view must be considered: the speed of growth and the absolute growth. Recently Pineau (245) has studied the linear (statural) growth of the human embryo. He gives the curve of rate of growth which shows, after a sharp increase, a progressive decrease all during gestation, and the curve of absolute linear growth which increases all during gestation (Fig. 5). We will emphasize growth measured by weight which is a little different, being more easily influenced. If we consider increase in mass per unit of time, or the rate of synthesis, we see that it is at first very large and then decreases progressively. For animals after birth, that decrease is well known, and the daily requirements per kilogram become lower and lower with age.

Minot (212) found that the rate of growth in the rabbit embryo, measured by percentage increments, decreased from the 9–15th day (when the rabbit adds, on the average, 70% to its weight daily) to the 15–20th day (when the average daily addition is only 21.2%). Then he estimated that over 98% of the original power of growth in the chick or rabbit has been lost at the time of hatching or birth. This is equally true in man. In all these cases growth follows an exponential law, as was illustrated recently by Laird et al. (164). Simultaneously, requirements diminished per unit of weight.

The speed of growth being maximum at the beginning, the metabolism is maximum and the requirements for energy or synthesis per unit of weight are also maximum, but because of the very small weight of the embryo the absolute requirements remain small. Nevertheless they must be satisfied because it is the sensitive period of organization.

With time, the absolute requirements change because the mass of embryo is increasing continuously. Absolute growth is represented by the actual weight which increases more and more with age. Beginning with a negligible weight the embryo acquires a weight of many grams in birds and may reach many kilograms in mammals. Schaeffer and Le Breton (275) have given the curve in chicken revealing the continued increase during incubation. The requirements are insured by the yolk and the albumen and their values depend on the previous feeding of the mother.

It is the same for mammals. The progressive evolution of weight in mammals has been studied many times in animals (guinea pig) and especially in humans. The weight of the embryo increases continuously during gestation and the requirements may become very large. Therefore correct feeding of the mother during all of gestation is very important.

Studying the curve of absolute growth of the human fetus in the second and third trimester, Gruenwald (123)

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emphasized the fact that growth, after following a straight line, declines (Fig. 6). According to the view of MacKeown and Record (191), it is the result of the limited possibilities of the supply line (mother and placenta). That ability declines strongly when a fetal weight of 3 kg is reached in the human. The proof is given by the reduced weight of the fetus when the number is increased, such as in the case of twins (123, 191, 218, 320). Some senescence of the placenta must also be envisaged.

REQUIREMENTS OF THE EMBRYO: DEFICIENCIES OR EXCESSES AND THEIR REPERCUSSIONS

In adults it was demonstrated that some definite proportions of fundamental nutrients (protein, lipid, and carbohydrate) were necessary. It was the same for vitamins and minerals. Correct equilibrium, advocated by Randoin and Simonnet (254), must be achieved also for mothers and their embryos. From this we can foresee that for embryos deficiencies and also some excesses have bad results. The case of phenylalanine is a good example; deficiency in the chick embryo and excess in the human fetus disturbs the developing neural system. It is essentially from the results of deficiencies that we have reached conclusions regarding the various requirements of embryos. We must keep in mind, however, that an excess may be deleterious, perhaps creating relative deficiencies.

General restrictions must be distinguished from specific deficiencies according to their results. General feeding restrictions have bad consequences on fertility of the mother and weight and survival of embryos, but specific deficiencies have worse results, since they alone are able to induce malformations. Thus it is necessary to distinguish these various types of deficiencies.

General deficiency. Dietary restriction, without any very specific deficiency, influences growth principally, but it may also induce prematurity or even death in mammals. Romanoff and Romanoff (263) have claimed that good reproduction in hens was dependent on the quantity of food. Byerly et al. (46) demonstrated clearly the relationship between egg laying and the feeding of the hen.

In the rat, dietary restriction reduced reproduction, introducing abortions during the beginning of pregnancy and above all on *day 8* (24). Recently Chow et al. (54) observed that dietary restriction during pregnancy and lactation resulted in permanent growth stunting, abnormal metabolism of nitrogen, and a diminished glucose tolerance. In sheep, Wallace (320) has demonstrated that fetal weight is less than normal when the diet is restricted (Table 1). Recently, in undernutrition in some Merino ewes, increased mortality of the embryos was noted (76).

In humans there are similar facts. Burke et al. (43) and Bourquin and Bennum (33) studied women with more or less deficient diets; the more deficient the diet, the more numerous were the deaths of the fetuses and the worse the overall condition (i.e., size and weight) of the newborn. Hendricks (130) has noted that the birth weight is higher in both white and nonwhite women who enjoy a favored economic status allowing good nutrition.

TABLE 1. *Influence of ewe feeding in twin pregnancy**

	Ewe, kg	144 day-old Fetuses, kg
High-level diet	91.4	3.00 and 3.36
Low-level diet	51.3	2.70 and 2.60

*Wallace (320).

In various countries subsisting on a low level of food intake and especially during the last war (Smith (285), in Holland), sterility, miscarriages, prematurity, and stillbirths were frequent, and an increase in malformations was discussed. A noxious influence on the nervous system was especially noted in correlation with myelination, a process beginning before birth in man and in many species (37, 334). In these human cases the dietary restriction was not absolutely general but involved primarily proteins and lipids.

In the rat, Barry (18), and in the rabbit, Galeeva (95) claimed that starvation induced stunted newborn or embryonic resorption. Malformations were not mentioned. The only exception is the observation by Runner and Miller (271) on the mouse, where 1 day without food induced abnormalities. Other repercussions must be envisaged. Kalter (156) has noted that with a hypocalorie diet, sensitivity to the teratogenic action of cortisone was increased.

Specific deficiencies. Thus general deficiencies often have various repercussions: prematurity, stunting, and death. Qualitative deficiencies limited to specific substances are much more serious. Not only can they prevent growth or induce death but many produce lesions and also malformations.

PROTEIN AND AMINO ACID REQUIREMENTS AND IMPORTANCE

Proteins as well as their amino acid constituents are of primary importance. According to Spratt (288), in chick embryo explanted to carbohydrate media containing no nitrogen sources, morphogenesis and cellular differentiation continued but there was no growth. For the chicken the nature of the protein of the food is important. Embryonic mortality is higher in eggs laid by hens on vegetable protein diets than it is in eggs laid by hens receiving protein of animal origin (46). For the maintenance of egg production in hens, Fischer (91) established that the following amino acids were essential: arginine, glutamic acid, histidine, lysine, leucine, isoleucine, tryptophan, phenylalanine, methionine, threonine, and valine.

Burke et al. (44) studied the results of pregnancies among many women living on various types of diet. Diets poor in protein yielded undersized and underweight newborn (Fig. 7). Donnely (74) has confirmed this observation.

In the rat, Guilbert and Goss (125) observed that diets containing less than 5% protein produced many abortions. According to Nelson and Evans (223), recently

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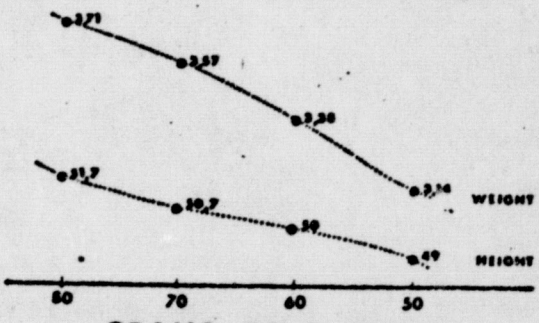

FIG. 7. Curves of growth (weight and length) in newborn infants as a function of protein intake of their mothers. Data for males and females are mixed. (Modified from the data of Burke et al. (44).)

confirmed by Hazelwood and Nelson (129), the abortions were the result of disturbances of the pituitary and ovarian functions, since a mixture of progesterone and estrone cured the condition.

Puppies born of protein-calorie deficient mothers are small, have poor survival, and coordination troubles correlated with neuroglial increase in the spinal cord (248). It was about the same for piglets (247).

The importance of each amino acid is not the same. In organotypic culture Wolff et al. (345) have noted that the requirements of various organs are not the same. Pigmentogenesis is facilitated by tyrosine and arginine (280). Herrmann (132) and Rothfels (266), with analogues of phenylalanine, induced abnormalities of the nervous system and, with analogues of leucine, abnormalities of the mesoblast (no somite formation). Feldman and Waddington (86), using ethionine as an analogue, and Waddington and Perry (318) induced abnormalities also in chick embryos cultivated in vitro. Austic et al. (13) and Grau et al. (121, 122), by perfusion of yolk sac, have demonstrated the importance of leucine and valine for the survival of the embryo, and of tyrosine for retinal pigmentation and the survival of the neural retina.

With a diet of 4% protein, poor in methionine and cysteine, MacLaren (192) observed abnormalities of the eye, especially of the lens, in the rat. Using ethionine as an antagonist to methionine, Lee et al. (174) and Proffit and Edwards (251) observed only a poor reproductive performance. The question of tryptophan is important because tryptophan is a precursor for nicotinic acid in various species. Alcock (5) and Albanese et al. (4) have reported disturbances with diets poor in tryptophan. Pike (243) has observed cataract. During embryogenesis in birds or mammals, synthesis of nicotinic acid from tryptophan was observed (12, 150, 338).

Excess of protein is not without repercussions. Aschkenasy-Lelu and Tuchmann-Duplessis (10) have noted that a diet very rich in protein is followed by sterility correlated to a disturbance of the ovary. Effects of injected supplementary amino acids may have no favorable effect. In birds the injection of glycine into the eggshell membranes (313) induced stunting, death, or abnormalities. With other amino acids or vitamins, no similar results were observed.

Cohlan and Stone (60) have observed analogous facts in the rat by intraperitoneal injection of amino acids. Excess of L-lysine and L-leucine diminished survival of the litter and the expected maternal weight gain. Injection of other amino acids has given the same results.

In the clinic, it is known that some amino acids in excess in the blood may be dangerous. In phenylketonuric children, the excess of phenylalanine due to lack of the correlative hydroxylase disturbs the evolution of their neural system involving its myelination (66) and impairing its normal function. The same metabolic error may exist in the mother. The elevated level of phenylalanine in her blood and its associated metabolic disorders, according to Fisch et al. (90), may have a detrimental effect on fetal growth and on its postnatal physical and mental development. Recently Mabry et al. (189) have observed six cases of phenylketonuric mothers. Their children do not have the abnormal gene and are not phenylketonuric but were mentally retarded. It was the result of the high level of phenylalanine in the mother's blood. Thus it is necessary to detect such mothers and to correct their metabolic disorder by a diet poor in phenylalanine.

LIPID REQUIREMENTS

In birds Menge et al. (204) have observed that polyunsaturated fatty acids in some foods improve reproductive performance; nevertheless the lipid content of the yolk follows very little the intake of the hen, which produces lipids from carbohydrates.

Female rats on a fat-deficient diet usually remain sterile or their embryos die. Burr and Burr (45) demonstrated that this was due to the lack of unsaturated acids and more precisely of linoleic acid. Evans et al. (82) and Maeder (196) confirmed these facts. According to Deuel et al. (72) the rat may become pregnant on a diet without lipids but its young cannot survive. With a diet poor in fat Martinet (200) observed localized hemorrhages in the fetuses due to linoleic acid deficiency.

The influence of an excess of cholesterol has been examined. Raulin (256) noted that in rats it did not modify the reproductive performance of females on a lipid-free diet, but if the diet contained nonsaturated lipids reproduction was clearly disturbed, the fetuses died, or their survival after birth was poor. In pregnant cats the injection of cholesterol (42) is followed by frequent cleft palate. In humans some metabolic disturbances increasing the level of lipids and especially cholesterol in maternal blood are perhaps responsible for developmental troubles. In diabetes there are premature births and an increase of malformations. The sugar level does not seem to be the problem. It is to be noted that according to Randle et al. (253) the fatty acids modifying glycolysis may play a role in diabetes

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by their excess. It is possible that the elevated level of lipids and cholesterol (71, 163) plays a teratogenic role.

Tuchmann-Duplessis and Mercier-Parot (310) have noted that a drug (Triton) which increases the cholesterol level in the blood induces abortions or abnormalities in mice and in rabbits. Conversely (267, 268) drugs (triparanol, AY 9944) which disturb cholesterol metabolism also cause perturbation of the developing embryo.

CARBOHYDRATE REQUIREMENTS

Carbohydrates are usually the first source of energy for embryos. According to O'Connor (231) this is the case for the synthesis of polypeptide chains, the first step in protein synthesis.

Spratt (289), who investigated the metabolism of the early chicken embryo explanted in vitro, reached the following conclusions. Carbohydrate is the main source of potential energy. The embryo is able to utilize some carbohydrates but not others, glucose and fructose being the best. The requirements of the various organs are not the same: brain, spinal cord, and optic vesicles will not develop at concentrations of sugar substrate which are quite adequate for the heart.

By perfusion of the yolk sac Austic, Grau and Matteson (13) have also observed the importance of glucose for survival.

The nature of the carbohydrate intake of laying birds deserves consideration. The nutritional value of the various carbohydrates depends on their nature. Couch et al. (63) fed birds on diets containing different carbohydrate sources. In some cases they observed a delay in the laying of eggs, and in other cases fetal deaths or anomalies similar to those in biotin deficiency, such as syndactylia and micromelia. They assumed that dextrin permitted synthesis of biotin in the intestine of the laying hen while sucrose and lactose did not.

According to Landauer (167), carbohydrate metabolism and its changes are very important for the developing embryo. This author believes that alteration of carbohydrate metabolism is responsible for the disturbances produced by insulin and toxins, a hypothesis confirmed by the fact that they are corrected by vitamin B.

An unexpected result must be noted: injection of glucose into the eggs may produce death and malformations (158).

For mammals, it is known that a special sugar, fructose, appears essential in relation to fetal life, a fact noted since 1859 by Claude Bernard. It is present in the blood of many embryos, especially in the ruminants (137). It has its origin in the placenta.

Certain sugars may be dangerous. Bannon et al. (15) have noticed cataracts in newborn rats resulting from the presence of galactose in the mother's diet. These facts were confirmed recently by Segal and Bernstein (278). Moreover, de Meyer (205) has seen many other malformations of the eye. In humans, it seems possible that some genetic galactosemic condition of a mother (55) may have repercussions on the embryo. It is possible that some disorders of carbohydrate metabolism in the mother such as diabetes are of importance for the fetus.

VITAMIN REQUIREMENTS

The study of this question was achieved by deficiencies of the vitamin studied in synthetic diets, and sometimes by addition of antibiotics to suppress vitamin production by the intestinal flora.

Frequently now antagonists are used; their action is quicker and permits intervention at the sensitive period, but the action is stronger, and perhaps there may be some toxic effect, since it is not always corrected by the vitamin. Moreover, this last method demonstrates the physiologic necessity of a substance, and its inhibition by an antagonist inducing various disturbances. But it does not indicate that it should necessarily be provided by the diet. Such seems the case for nicotinic acid usually synthesized in many species.

In this field, as in the case of minerals, the question of an equilibrium is important: the relationships between calcium and phosphorus and between calcium and vitamin D have been known for a long time. The relations between pyridoxine and nicotinic acid, pantothenic acid, and even unsaturated fatty acids must be noted. A complete review of vitamin interrelations is given by Terroine (301).

The question of very specific deficiencies is also important. Comparing the results of a specific pantothenic acid deficiency with a complete vitamin B deficiency, we have noted that the former was the more noxious. The resorptions were approximately the same, but the malformations were much more frequent (108). In contrast to the lack of a vitamin, its excess may be noxious either by imbalance or by itself. This is particularly the case with vitamin A.

Ascorbic acid. For ascorbic acid, its presence in the diet is only necessary for species such as guinea pig, monkey, and man, which do not synthesize it. Cheadle et al. (52), Mouriquand et al. (216), and Reyer et al. (259) found such young newborn guinea pigs developed scurvy. In chicken embryo which synthesizes ascorbic acid, Fabro and Rinaldini (85) have noted a reduction of synthesis with age. In humans, premature birth has been suggested to be related to this deficiency by Martin et al. (199).

Thiamine, vitamin B_1. In the chick embryo, Naber et al. (217) increased the death rate by antivitamins (neopyrithiamine and oxythiamine). In the rat, Nelson and Evans (225) have observed similar facts, but thought the abortions occurring in the latter experiment to be due to hypophysogenital disturbances. With a diet poor in thiamine, Brown and Snodgrass (38) noted in the rat a reduction of the litters but no malformations. In sows, Ensminger et al. (78) also reported disturbances of pregnancy. In humans, where beriberi is frequent, there is no indication of the production of malformations.

Riboflavin, vitamin B_2. The influence of lack of vitamin B_2 (riboflavin) on reproduction is well marked. Disturbances due to its deficiency have been observed in birds.

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There is a great reduction of the hatching rate, and often the limbs of the embryos are shortened. Edema, anemia, and dwarfism were also noted. Lepkovsky et al. (178) and Brown (40) demonstrated the importance of transfer of riboflavin from the egg to the embryo.

In the rat, Warkany and Schraffenberger (329) established that a riboflavin-deficient diet has a true teratogenic effect. This deficiency induces definite malformations: cleft palate and shortening of the limbs with syndactylia (Fig. 8). Giroud and Boisselot (104) and Bologna and Piccioni (29) obtained similar results with a synthetic diet deficient in riboflavin. In a deficiency produced by an antagonist (galactoflavin), Nelson et al. (221) and Kalter and Warkany (157) observed much more varied abnormalities. In humans it appears that only one case was quoted and may be questioned.

Nicotinic acid, vitamin P-P. In the chicken, nicotinic acid is presumably synthesized during development (69). Nevertheless, according to Briggs et al. (36) giving the hens a large amount of bone ossein in a purified ration creates an amino acid imbalance and reduces egg production and hatchability. They interpreted the result as a nicotinic acid deficiency because nicotinic acid produced a recovery. Clear-cut evidence that nicotinic acid is an important metabolite was given by Ackermann and Taylor (2). Using 3-acetylpyridine as an antagonist to the vitamin, these authors obtained slowed growth, malformations of the feet, and edema. With 6-aminonicotinamide as antagonist, Landauer (169) has observed micromelia and parrot beak. These could be prevented by nicotinamide.

FIG. 8. Malformations in riboflavin deficiency. Cleft palate (top), micromelia (bottom), and syndactyly (middle). (According to Giroud and Boisselot (104).)

In the rat, Ruffo and Vescia (270) have noted a reduction of litters in deficiency. After injection of 6-aminonicotinamide, Chamberlain and Nelson (49) have observed many abnormalities. Analogous facts were observed in mice (246). Many experimental observations have been made with antagonists. They prove the important function of nicotinic acid, but perhaps did not prove that it is a necessary nutrient, since many species seem able to synthesize it from tryptophan. On the other hand, we must note that in humans there is no evidence that this deficiency produces anomalies in man, in spite of the prevalence of pellagra in many countries.

Pyridoxine, vitamin B_6. Experiments on laying hens involving a vitamin B_6 deficiency revealed a critical need for this vitamin, since there was a rapid decline in egg production (65). The antivitamin exerts an inhibitory effect on the developing chick embryo: death or retardation but no abnormality (61). In humans, a deficiency of this vitamin has been suggested by the fact that vitamin B_6 is effective in the treatment of vomiting in pregnancy (331, 335).

Experiments have shown that abortions are common in animals suffering from pyridoxine deficiency. Ross and Pike (265) observed a deleterious influence of this deficiency on the development of the embryo. Nelson and Evans (224) obtained abortions with an analogue (deoxypyridine), possibly by a secondary impairment of hypophysogenital function, since administration of folliculin and progesterone restored normal gestation.

Folic acid. Folic acid appears to be very important possibly by way of its role in deoxyribonucleic acid synthesis (participation in thymine synthesis and other purine bases). Recently Potier de Courcy (250) showed this role and its influence by the decrease of DNA phosphorus, RNA phosphorus, and protein nitrogen in the rat fetus during this deficiency.

In the reproduction of birds, the part played by folic acid was demonstrated by Taylor (299), its absence in the diet increasing the mortality of the embryo. Moreover, folic acid deficiency appeared teratogenic. Sunde et al. (292) found angulations of the tibiotarsus, syndactylia, and parrot beak.

In the rat, Richardson and Hogan (260) as well as Hogan et al. (136), observed that with an incomplete synthetic diet, 1.7% of the young were hydrocephalic. This was partly suppressed by addition of folic acid, and completely suppressed by addition of vitamin B_{12} (233). Stempak (289), with a folic acid-deficient diet limited in time, observed the same abnormality. Nelson and Evans (223), with a diet made deficient by an antag-

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FIG. 9. Folic acid deficiency in the rat. Malformations at the various dates of treatment with X-methylfolic acid during gestation. (Modified from the data of Nelson and Evans (223).)

onist, found complete resorption of embryos. Thiersch et al. (303) obtained similar results with aminopterin. Giroud and Lefebvres (106) with a deficient synthetic diet showed its teratogenic action in the rat. With severe deficiency there were resorptions of the embryos but with less severe deficiency they obtained a series of malformations (Fig. 9).

With antivitamins, teratogenic action was also obtained. Using X-methylfolic acid, Richardson and Hogan (260) obtained 20% hydrocephalus. Nelson et al. (220, 227) observed various types of malformations in experimentally induced deficiency. Abnormalities of the urinary tract (211) and of the circulatory system were noted by Baird et al. (14). Death or abnormalities, according to the stages of administration, were observed also by Baranov (16). Tuchmann-Duplessis and Mercier-Parot (309) and Tuchmann-Duplessis and Lefebvres-Boisselot (308) obtained abnormalities with X-methylfolic acid in other species, the mouse and the cat.

Some significant interactions between a folic acid antagonist, pyrimethamine isothionate, and solvent were observed by Anderson and Morse (9), and folic acid did not correct the teratogenic activity. In humans, the deficiency produced by an antagonist appeared teratogenic. Thiersch (302) observed one anencephalic newborn consequent to administration of aminopterin. Warkany et al. (325) and Hibbard (133) confirmed the fact. Hibbard and Smithells (134) found a significant relationship between malformations and defective folate metabolism. A folic acid deficiency seems easy to produce during human pregnancy; anemia or megaloblastic bone marrow changes appear revealing (184). The prevention of low blood folate by various doses of folic acid indicates that the daily requirements are around 0.5 mg (185). Willoughby (337), from levels observed in the blood, concluded that in late pregnancy the requirements are close to 0.3 mg/day.

Biotin. Biotin does appear necessary. In the hen, biotin deficiency results in a rapid decline of hatchability of the eggs (65) and the appearance of gross developmental abnormalities: parrot beak, crooked tibiotarsus, and short twisted tarsometatarsus.

In the rat this deficiency does not seem teratogenic, but deaths or resorptions were noted by Giroud et al. (107). With a deficient diet continued for a long time, Cooper and Brown (62) also found many resorptions of embryos, and in the survivors only lesions of the heart and the liver.

Pantothenic acid. In birds the importance of pantothenic acid in reproduction was observed by Bauernfeind and Norris (20), Taylor et al. (300), and Gillis et al. (101). With antagonists the same results were obtained. Goetinck, Abbot and Kratzer (115) with ω-methyl-pantethine injected into the egg, observed high mortality and retarded development of the brain and neural cord.

In the rat analogous data were noted by Nelson and Evans (222). Lefebvres (175) using a completely synthetic diet without pantothenic acid proved the teratogenic role of that deficiency: abnormal embryos, as well as dead or resorbed ones were found in the litters. Anencephaly, exencephaly, and anophthalmia were noted, but other more typical anomalies were also observed such as vascular alterations, with stases at the extremities of the limbs leading to the destruction of the fingers (109) (Fig. 10). Addition of ascorbic acid lessens the teratogenic action (Lefebvres-Boisselot and Cero (176)). Coggi (58), working on mice, observed only resorption or stunted embryos with pantoyltaurine. Also in the rat Zunin and Borrone (350) using pantoyltaurine, and Nelson et al. (228) using methyl-pantothenate obtained many abnormalities. In the guinea pig, Hurley et al. (144) have observed the increase of pantothenic acid and coenzyme A levels in normal embryos and noted the sensitivity of the female to deficiency. They have seen

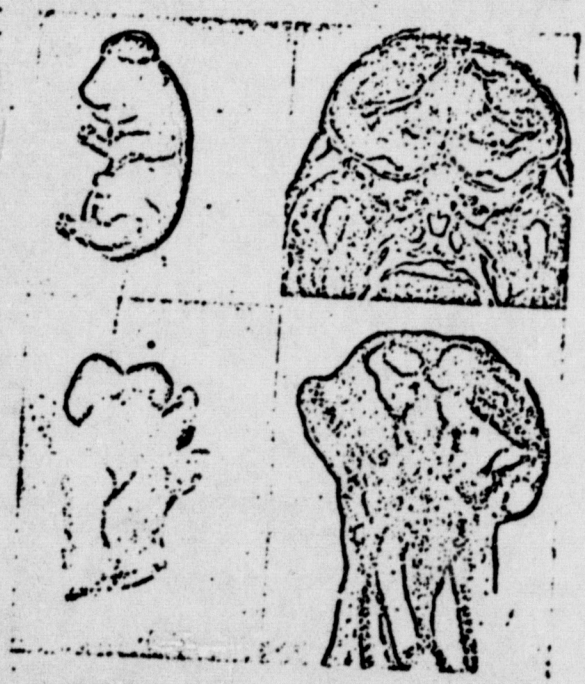

FIG. 10. Malformations in pantothenic acid deficiency. Exencephaly and anophthalmy. Vascular alterations in the limbs followed by ectrodactyly. Note the destruction of digital bones. (According to Giroud et al (109).)

that a late transitory deficiency induces many deaths or abortions.

The influence of an excess of pantothenic acid was investigated. Vacca et al. (314) have noted its favorable influence on growth and differentiation of the embryo.

Vitamin B_{12}. Vitamin B_{12} appears necessary for reproduction. Perhaps it is because of its action on nucleic acid metabolism correlative with that of folic acid (332). Some of this interaction may occur because vitamin B_{12} deficiency hampers the biogenesis of the active forms of folic acid such as tetrahydrofolic acid.

In poultry, Lillie et al. (181) noted that vitamin B_{12} deficiency disturbed reproduction. Olcese et al. (234) and Milligan and Combs (209) observed hemorrhages and myoatrophies in addition to mortality. Ferguson et al. (68) noticed alterations of the heart, liver, brain and spinal cord, as well as edema. By injecting an antimetabolite into the eggs Ransdell (255) inhibited the hatching.

In rats, O'Dell et al. (233) have observed that hydrocephalus from nutritional origin was prevented partially by folic acid but completely by vitamin B_{12}. In the same deficiency, Jones et al. (152) have found only lesions of the heart, liver, and brain. In the mouse, according to Jaffe (151), reproduction was maintained but further development was hampered. Recently Woodard and Newberne (346) have studied this deficiency in the rat. They have noted very low levels of vitamin B_{12} in the livers with the deficient diet. They observed 14% hydrocephalus and some other abnormalities. Addition of monobasic acids of vitamin B_{12} caused infertility. The addition of X-methylfolic acid restricted the litters, and hydrocephalic embryos with umbilical hernia and limb abnormalities were produced.

In a strain of mice with a high incidence of abortion B_{12} is able to correct the situation (173). In humans (283), a favorable influence of vitamin B_{12} on the developing premature was noted.

Para-aminobenzoic acid. Concerning para-aminobenzoic acid very little is known. In organ cultures, Kieny (159) and Wolff (344) recognized its growth-stimulating power for the cartilaginous anlage of the tibia.

With massive doses of para-aminobenzoic acid or inositol, Ershoff (79) did not notice adverse effects.

Carnitine. Liebecq-Hutter (180) pointed out the favorable influence played by carnitine or vitamin B_T in bone development. Kieny (160) claimed the same for dicarnitine as well as for carnitine; high concentrations of these growth factors were able to replace *p*-aminobenzoic acid.

Choline. With a diet deficient in choline, Jukes (154) observed in the chicken and the turkey a thickening of the leg bones. In piglets according to Ensminger et al. (78) choline deficiency caused a lack of motor coordination and a high postnatal death rate. In the rat, Meader (203) noted accumulation of fat in both fetal and maternal livers. Some interactions must be noted between choline and vitamin B_{12}. When the B_{12}-deficient diet is also deficient in choline, the deleterious action is increased and the addition of methionine or sarcosine, in equivalent methyl groups, did not improve the condition (346).

Vitamin A. In the laying hen, the dietary content of vitamin A is of great importance (241, 319). The vitamin A content of the egg is clearly increased by enriching the diet with the vitamin. MacClymont and Hart (190) described the deleterious effect of vitamin A deficiency on egg production, hatchability, and chick viability.

In mammals, the repercussions of vitamin A deficiency on reproduction were observed long ago. In the sow the number of stillborn was twice as high in the deficient animals as in the controls. Hale (126) demonstrated the teratogenic action of this deficiency. In addition to dead or stunted embryos, he observed many malformations in piglets: anophthalmia or microphthalmia, harelip, cleft palate, external ear anomalies, and fusion of both kidneys (horseshoe kidney). These observations were confirmed by Goodwin and Jennings (117) and by Palludan (238). This last author moreover observed metaplasia of the mucous epithelia.

In the calf, Wolbach and Bessey (342) and Moore et al. (213) observed eye atrophy due to compression of the optic nerve at its cranial exit.

In the rat, Andersen (7) noticed that vitamin A deficiency caused diaphragmatic hernia. Warkany and Schraffenberger (328) described a series of malformations

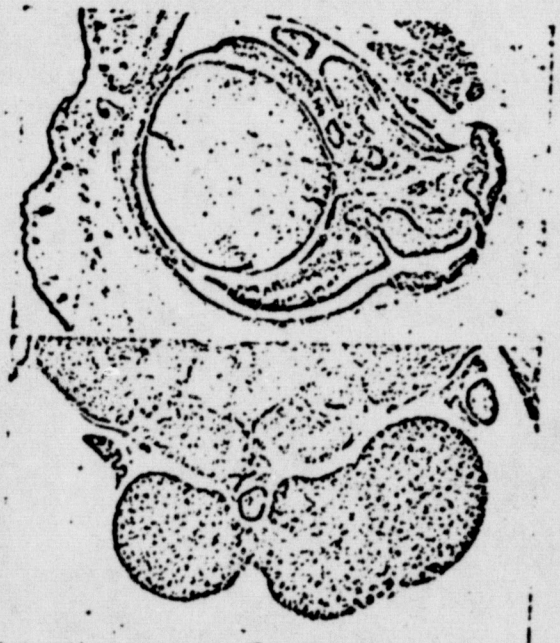

FIG. 11. Malformations in vitamin A deficiency. Abnormalities of the eye (coloboma, fusion of cornea to eyelids, fibrosis of corpus vitreum), and horseshoe kidney. (According to Roux et al. (269).)

in the young from mothers deficient both in vitamin A and carotene. Many malformations were localized to the eye (coloboma, lack of anterior chamber, fibrosis of the vitreous body). Wilson and Warkany (339, 340) have reported experiments in which 75% of the embryos were abnormal. They described many abnormalities of the urogenital apparatus. The kidneys remained confined in the pelvis and fused together, the male genital apparatus had a tendency to intersexuality; the urethral groove of the penis remained open (hypospadias), and the Mullerian canal did not resorb. Anomalies of the large vessels (especially aortic arches) and of the heart were also observed (Fig. 11). Roux et al. (269) have seen the same abnormalities. It should be added that the fetus may show lesions characteristic of the adult deficiency such as keratinization of mucous epithelia.

In other species, particularly in the rabbit (206), the teratogenic action of vitamin A deficiency was also observed. In humans only one case seems to have been quoted (274) and it is open to question since Venkatachalam et al. (316) did not notice any repercussions in mothers very poor in vitamin A.

High doses of vitamin A are teratogenic as was observed by Cohlan (59) and by Giroud and Martinet (112). The influence of stage of development is very clear. It induces death during the 1st day of gestation and is teratogenic only from the 8th to the 13th day, the type of malformation (113) also depending on the stage. Usually 50,000 IU/rat were given but 1,000 IU are still teratogenic. Even at high doses the concentration of the vitamin in the fetus was only twice that of the control (105) (Fig. 12).

In the hamster, hypervitaminosis A produced changes in the mesoderm of the embryo followed by necrosis (198).

This action is not the same for different species: rats and mice appear very sensitive, much more than guinea pigs and rabbits. Vitamin A does not seem to be teratogenic in humans; until now nothing has been cited in the literature, except for one case. Pilotti and Scorta (244) recently recorded that a mother who had taken high doses of vitamin A during the early stages of her pregnancy had a child with urinary malformations analogous to those observed experimentally.

In vitro, an excess of vitamin A disturbs epidermal differentiation. Lawrence et al. (171) have observed that in hamsters it produced a mucous metaplasia of the epidermis similar to that observed in birds by Fell (87). It is the reverse of what is produced by the deficiency.

FIG. 12. Malformations of excessive vitamin A according to the stages of treatment. (According to Giroud and Martinet (113).)

Vitamin D. Vitamin D appears necessary for reproduction. Its deficiency is not truly teratogenic: it induces only rickets in the embryo, as in the young animal.

Insko and Lyons (148) claimed that a deficiency in hens induced the death of embryos; according to Branion and Smith (35), its excess is also noxious.

In foals, calves, and dogs, Chavanac (58) recorded the occurrence of rickets. The importance of this vitamin is certainly related to the calcium and phosphorus supplies. In cattle, Wallis (321) observed that in dairy cows the feeding of a vitamin D-deficient diet resulted in hypophosphatemia and hypocalcemia, stiffness, and spontaneous fractures; their calves appeared rachitic.

Grant and Goettsch (120) found a greater tendency to rickets in rats born from mothers receiving a diet poor in calcium and in vitamin D.

In the same animal and on a diet poor in calcium, Swanson and Iob (294) observed that the fetuses get nearly normal quantities of these substances, when vitamin D is given. Warkany (323) after a long-continued deficient diet observed that many fetuses were stillborn or stunted. Moreover, he observed alterations of the skeleton in about 45%: pronounced curving of the radius, ulna, tibia, and fibula, as well as an abnormal angulation of the ribs. The histological lesions were nevertheless somewhat different from rickets.

Vitamin D excess is probably not innocuous. In the clinic, abnormal calcification of the skull in the newborn was observed after unusual doses of vitamin D. Experimentally, Friedman and Roberts (94) have observed supravalvular aortic stenosis in offspring of rabbits whose mothers received high doses of vitamin D. Their experiments demonstrate also the crossing of the placental barrier by vitamin D.

Vitamin E. The importance of vitamin E for reproduction was discovered in 1922 by Evans and Bishop (81). In the chicken Adamstone (3) observed that the deficiency caused lesions of extraembryonic vessels leading to death. In the turkey, Ferguson and Couch (89) noticed opacity of the lens and hemorrhages into the vitreous body.

In the rat, Evans and Bishop (81) showed that vitamin E deficiency caused the degeneration of placental vessels, leading to embryonic death. Mason (202) and Suomalainen (293) confirmed this. William et al. (336) found that newborn lambs were affected by muscular alterations. Callison and Orent-Keiles (47) found ocular alterations somewhat similar to retrolental fibroplasia.

True malformations resulting from vitamin E deficiency were observed in the rat by Thomas and Cheng (304) and Cheng et al. (53). After a long-continued deficient diet and after preventing death of the embryos by late additions of a little vitamin E, they obtained a whole series of malformations: umbilical hernia, hydrocephalus, exencephaly, cleft palate, harelip, ectocardia,

and anomalies of the tail and other parts of the skeleton. Using the same technique Gortner and Ekwurtzel (118) did not observe such a severe teratogenic action on other strains, in fact, less than 5% of the embryos were abnormal.

It has been noted that the level of vitamin E is low in premature newborn infants. Some hemolytic anemias are related to this condition since they are corrected by 9 mg of α-tocopherol according to Oski and Barness (237). In a strain of mice, vitamin E was able to suppress spontaneous abortion (173).

Vitamin K. Vitamin K appears necessary, but its lack is not truly teratogenic. Vitamin K deficiency may play a part in the genesis of some human fetal hemorrhages, but this fact is still debatable (249).

In the dog, according to Moore et al. (214), vitamin K deficiency is responsible for retroplacental hemorrhages followed by abortions. Brown et al. (37) showed that cerebral hemorrhages were found in newborn rats when vitamin K and lard were absent from the mother's diet. Under the same conditions Hilber and Freisiederer (135) saw myocardial lesions.

We must note that experimentally dioxycoumarin, an antivitamin K, induces hemorrhagic lesions and abortions (162, 252), and in man the same results were observed (295, 306).

INORGANIC SUBSTANCES

The inorganic substances also have great importance. Some facts have been known for a long time, but today many suggestive ones are revealed.

Calcium and phosphorus. Calcium is very important for the general development and calcification of the skeleton. In the first stages of embryogenesis calcium is necessary (68). In birds, lack of calcium decreases the egg production (41). Hart et al. (127) observed that cows on a diet poor in calcium produced immature, stillborn fetuses. This was also noted by Hart and Steenbock (128) in the sow, and by Macomber (194), Cox and Imboden (64), and Bodansky and Duff (28) in the rat.

If the calcium content of the diet is diminished, calcium and phosphorus disappear from the tissues of the mother rat (281) and additional calcium is required to prevent this, both in rats and humans. According to Toverud and Toverud (307) the ossification of the human fetus is dependent on the dietary calcium and phosphorus content. If it is low, rarefaction of bones and teeth occurs (30). Vitamin D improves the condition. Injection into the yolk sac and allantois of small doses of calcium pantothenate and calcium chloride induced malformations notwithstanding that the calcium level in the plasma of the embryo was depressed (119).

Recently calcium and phosphorus transfer was measured by radioisotopes: in the cow near term the transfer was, respectively, 5.3 g and 2 g/day. It was strongly increased during lactation (296).

Magnesium. Sell et al. (279) have studied magnesium deficiency in the hen and concluded that 30 mg/day are necessary for good reproduction. Tufts and Greenberg (311) claimed that magnesium requirements are connected with the calcium content of the food. With a diet containing 0.87 mg calcium/100 ml, 5 mg magnesium were necessary to ensure growth of the rat: female rats fed on this diet gave birth to young of normal weight. With the same magnesium content and 1.16 mg calcium/100 ml, they remained sterile.

Excess magnesium did not have an adverse influence, even if the level was doubled in the mother's tissues (161).

Sodium. According to Miller (207) gestation is normal with a diet containing 0.45% of sodium, but the results are more satisfactory with 0.53% according to Olson and St. John (235). With a very low content (0.002%) Orent-Keiles et al. (236) did not obtain normal pregnancies; only 2 rats out of 12 became pregnant and they did not bring their litters to full term. Philips and Sundaram (242) studied physiological modifications resulting from sodium depletion of the mother.

Thus a minimum amount of sodium is necessary for normal gestation. But sodium excess appears to be harmful to the mother and to the fetus when we consider some clinical cases.

In humans, a diet poor in sodium chloride partially prevented hypertension or toxemia which reduces the placental flow by alteration of the spiral arteries of the myometrium (73). This condition results in small malnourished babies (92).

Potassium. With a very low potassium content in the diet, Heppel and Schmidt (131) observed in the rat that gestation is possible but that the mothers did not bring up the young, often eating them at birth.

Prolonged ingestion of potassium metabisulfite depresses the fertility of the rat, and decreases the number of young in the litter (56).

Iron. Iron is necessary for the building of hemoglobin. A deficient diet, maintained during successive generations induces a progressively anemic condition in the young rat (6). According to Reid and MacKintosh (257, 258) and Napier and Edwards (219), however, the viability and the strength of the newborn are diminished by the mother's anemia.

In humans Bothwell, Pribilla and Finch (31) claimed a withdrawal of iron at the expense of the mother, whose hematopoietic activity is reduced.

Iron is accumulated from the 7th month by the human fetus and correlatively disappears out of the mother's liver (11).

Chanarin et al. (50) claimed that iron deficiency facilitates folic acid deficiency during gestation. Lowenstein et al. (184) question this idea but believe that pregnancy enhances an iron and folic acid deficiency.

Copper. Ewes fed on a diet deficient in copper may give birth to abnormal lambs (22, 75). The newborn are unable to stand or to obtain milk from their dams. Those that were able to get up, swayed and collapsed, and their hindquarters seemed paralyzed, thus the condition was termed "swayback." Widespread symmetrical degeneration was found in the white matter of the spinal cord. Innes (147) considered that the disorder seemed

to be essentially a process of demyelination. Instances of swayback have been observed in various countries. Palson and Grimson (239) have seen it when sheep in Iceland were fed with seaweed. In this case, the copper content of the mother's blood was one-fifth of the normal and that of the lamb's liver 20–30 times lower than the lower average. Some skeletal alterations in the young animals have also been observed.

The human fetus accumulates copper as it does iron and the mother's stores become depleted (11).

Molybdenum. Molybdenum which is a component of xanthine oxidase has been recognized as being required for growth of poultry (172). In the ewe, an excess induces a process of demyelination in the newborn (210).

Iodine. Hart and Steenbock (121) and Smith (285) noticed that in countries poor in iodine piglets have hypertrophied thyroids and a hairless skin. Stillborn births and very weak young were also frequent. Similar alterations were also observed in goats (201).

In humans analogous observations are made in populations living in countries poor in iodine. In such areas, stillbirths and neonatal deaths are more numerous than usual. The newborns have hypertrophied thyroids, very often they develop cretinism, and deafness and speech defects are almost constant. Lotmar (183) studying the brain, found irregularities in the development of the various cortical layers and variations of the nerve cell distribution. According to Eggenberger (77) of Switzerland, the percentage of abnormalities is 1.45 %, instead of 0.4 % which is the normal figure. When the population was given iodine, goiters disappeared and the percentage of abnormalities dropped to a normal level.

Jovanovic and Pantic (153) demonstrated the influence of iodine on reproduction in rats bred on a goitrogenic soil; the female whose diet was poor produced reduced litters.

On the other hand, excess iodine is also noxious. This was seen after treatment of women with high doses of iodine. The result was goitrous infants, with hypothyroidism or hyperthyroidism; some also had permanent mental retardation (25, 26, 67, 240, 261).

Fluorine. Fluorine appears necessary for the calcified tissues, especially the teeth, a tendency to caries being the result of a deficiency.

These bad results can be observed at any time on teeth which develop in the fetus or even after birth. The fluoride content of bone and especially teeth increases with age, but there are limited levels of fluoride metabolized from drinking water since in fluoride-rich areas the uptake is not significantly greater than in other areas. Gedalia et al. (97–99) have studied the active role of the placenta in fluoride transfer. According to Yaeger (347), the developing incisor of the rat is altered by high-fluoride diets.

Manganese. Manganese is indispensable to reproduction, but it seems also that it plays a role in the mineralization of bones (287, 317). Gallup and Norris (96) have observed that a manganese-deficient diet in the hen is followed by a high death rate of the embryo. Landauer (166) had observed chondrodystrophy (short and thickened limbs, parrot beak) produced by a deficient diet: Lyons and Insko (188) identified manganese as the missing factor. Caskey and Norris (48) obtained ataxic chickens or chickens with micromelia when the hens were submitted to a diet very poor in manganese.

In the rat, Barnes et al. (17) observed tibial shortening and bowing. Hurley (140, 142, 145) [illegible]d in the rat, mouse, and guinea pig the abnormalities of the skeleton which include specific epiphysial dysplasia. But, above all, she demonstrated that the offspring were affected by an ataxic condition, incoordination, lack of equilibrium, retraction of the head, and correlatively, underdevelopment of the vestibular portion of the inner ear. Studying successive generations with the deficient diet, Hurley (80, 142) has observed the increase in the frequency and the setiousness of the syndrome, which naturally the manganese intake suppresses. One microgram of manganese per gram of dry diet is inadequate for the pregnant rat (145). Samofal (273) claimed the deficiency induced cretinoid newborns, otherwise that excess of manganese in rats disturbs tooth formation.

The transfer of ^{54}Mn by placenta is very quick, its maximum being on the 15th day (262). In calves some limb alterations were noted with low-manganese rations (23).

Zinc. Zinc is found in the egg, but little is known about its importance. Nevertheless it should not be overlooked that zinc is a trace element associated with many enzymes: carbonic anhydrase, carboxypeptidase, several dehydrogenases, and alkaline phosphatase.

Turk et al. (312) noted that a zinc-deficient diet in the hen induces weak and dying chicks. Blamberg et al. (27) showed its deleterious action especially on the skeleton, but also on the neural system. O'Dell (232) recently studied the correlations between zinc and various nutrients.

In mammals zinc also appears necessary. It was seen at first on suckling mice (229). But recently Hurley and Swenerton (143) have demonstrated its necessity for the embryo, by using a very defined deficient diet and by eliminating all causes of environmental contamination. A short deficiency is sufficient to induce almost immediately a low level of zinc in the embryo, and to determine death, slowing of growth, and to produce many malformations especially in the skeleton and in the neural system.

Nickel and cobalt. The requirements are not known, but the presence of these elements in some organs suggests that they must be provided.

Strontium. Some alterations of dentinogenesis have been noted after injection of strontium (348).

GENERAL CONSIDERATIONS ON THE REQUIREMENTS

We have seen the bad results of various deficiencies and we have noted that usually very specific mild deficiencies are sufficient to induce malformations.

All the facts previously cited indicate the necessity of

TABLE 2. *Diet used for pregnant rat**

Constituents per 100 g of Diet	
Three times alcohol-extracted casein	17.5
Cystine	0.1
Sucrose	64.9
Margarine	5.0
Peanut oil	5.0
Salt mixture (Hubbel et al.)	4.0
Cellulose	2.0
Vitamin mixture	0.5
Sulfamide	1.0
0.5 g of Vitamin Mixture Contained in milligrams per 100 g of Diet	
Thiamine	1.2
Riboflavin	1.2
Pyridoxine	1.2
Pantothenic acid	3.0
Nicotinamide	15.0
Biotin	0.02
Vitamin K	0.5
Vitamin B_{12}	0.003
Inositol	20
Para-aminobenzoic acid	30
Vitamin E	20
Folic acid	5.0
Are added separately per 100 g of diet:	
Choline	100 mg
Vitamin A	1,000 IU
Vitadone	0.02 ml
Vitamin D	200 IU

* Potier de Courcy (250).

TABLE 3. *Nutritional requirements of premature infants*

Water	
Energy	150 cc/kg
Protein	120 cal/kg
Carbohydrate	5 g/kg
Fat	18 g/kg
Calcium	2 g/kg
Phosphorus	160 mg/kg
Vitamin A (fatty solution)	130 mg/kg
Vitamin D (fatty solution)	15,000 IU
Vitamin C (fatty solution	3,000 IU
	50 mg

(From Levine and Dann (179).)

many substances for the embryo, but frequently do not give quantitative indications about their various requirements. Many notions in the literature about requirements concern only the young and the adults and often we must calculate those of embryos or of their mothers.

The question is difficult. Many requirements are influenced by other constituents of the diet: some increase and others diminish them. The importance of an equilibrium stated by Randoin and Simonnet (254) many years ago must not be underestimated.

We know overall that in the embryo the requirements by weight unit are larger than those of the adult, and that the requirements of a pregnant female are sharply increased.

TABLE 4. *Nutritional requirements of women**

	Normal	Pregnancy, 4-9th month
Calories	2,100	2,500
Protein, g	60	85
Calcium, g	0.8	1.5
Iron, mg	12	15
Vitamin A, IU	5,000	6,000
Ascorbic acid, mg	70	100
Thiamine, mg	1.1	1.1
Riboflavin, mg	1.5	2.5
Nicotinic acid, mg	1.1	1.8
Vitamin D, IU		400-800

* National Research Council.

TABLE 5. *Nutritional requirements of the cow**

Cow, 454 kg	Normal	Pregnancy
Calories	6,400	11,800
Protein, g	270	544
Calcium, g	10	22
Phosphorus, g	10	17

* FAO.

TABLE 6. *Nutritional requirements of the sow**

Sow, 45 kg	Normal	Pregnancy
Calories	3,500	4,100
Protein, g	360	420
Calcium, g	14	16
Phosphorus, g	9	11
Carotene, mg	4	20
Vitamin A, IU	2,600	13,000
Vitamin B_1, mg	2.5	3.0
Vitamin B_2, mg	3.8	3.8
Vitamin P-P, mg	12.5	12.5
Vitamin D, IU	250.0	300.0

* FAO.

Birds. Since the stocking of nutrients for bird embryos is done in advance it is necessary that the feeding of the laying hen should be good. Usually a hen gets 70–80 g food/day (carbohydrate 97.7 %, protein 2.1 %, and lipids 0.7 %). During the laying period it must receive 124–135 g. According to Byerly (46), there is a clear correlation between feeding and laying.

Mammals. We know some correct diets used for experiments on the pregnant rat (Table 2).

Premature infants, more precisely those born before term, can yield instructive data concerning the requirements of the fetus: they are constitutionally fetuses, and we can study the balance of the intake and of the output as in a free organism. Unfortunately, under the label of "premature," infants born before term and those undernourished are usually confused. Notwithstanding these difficulties, the observations of Levine and Dann (179) are interesting from this point of view (Table 3).

We must cite the recommendations of the National

Research Council for women and of the FAO for the cow and the sow, normal or pregnant (Table 4).

For folic acid and vitamin B_{12} we can add some precision. Daily addition of 0.5 μg of folic acid determines the rise of folate level in the serum, it indicates that this dosage may well be above the minimal requirements (184). Willoughby (337) testing the folic acid level in the blood concluded that the minimal oral requirements in late pregnancy are close to 0.3 μg/day. According to Lowenstein et al. (184), daily addition of 5 μg of vitamin B_{12} did not affect the serum level, and perhaps is under the minimal requirements.

For some minerals, Leonov (177) has recently made a study on the requirements of the pregnant woman (Tables 5 and 6).

REPERCUSSIONS OF ABNORMAL NUTRITIONAL CONDITIONS

The most studied repercussions of abnormal nutritional balance concern the deficiencies. We have noted previously some disturbances due to excess; they seem less frequent, but their results are similar to those of deficiencies.

Deficiencies may act by insufficiency of building material, by deficiency of energetic substances, and above all by enzymatic disturbances. The last factor must be envisaged especially for induction or differentiation processes where the integrity of the cells is the most necessary.

Since many cell enzymes derive from vitamins it is possible to see that deficiencies bring about disturbances of cell function in that way. In riboflavin deficiency, Miller et al. (208) have demonstrated that, at the teratogenic stage, there is a serious drop in flavin adenine nucleotide (FAD). For some deficiencies (folic acid, vitamin B_{12}), nucleic acid disturbances may be involved.

Alterations of chromosomes with their secondary results may also be seen. For nicotinic acid deficiency there are abnormalities of chromosomes according to Ingalls et al. (146). In riboflavin deficiency according to Warkany et al. (330) there is no modification of chromosomes. In cases of excess the same hypothesis is possible. Tamboise and Tamboise (297) have not clearly seen chromosome abnormalities with excess of vitamin A. Death of some differentiating cells may also be a mechanism of abnormal development.

The general deficiencies (restricted diets) may be followed by death of the embryo, its prematurity, or only by slowing its growth. By example, in our riboflavin deficiency the embryos achieve only four-fifths of their normal weight.

Specific deficiency of a nutrient may give the same results, and moreover, may produce some characteristic lesions and malformations. Their type and their importance vary according to the nature and the magnitude of the deficiency. Very slight deficiencies act only on growth: they slow it. Small deficiencies may induce abnormalities. Severe ones are followed by death or resorption of the embryo.

Tissue alterations. Malformations are the most spectacular repercussions of deficiencies, but there are other disturbances of the developing embryo which may be produced. They are common tissue alterations analogous to those of pathological anatomy such as anemia, edema, hemorrhages, and necrosis. For example, biotin deficiency can induce necrotic liver and heart (62).

There are also specific alterations. From time to time, in cases of vitamin deficiency some lesions are produced similar to those of the deficiency in the adult: rickets (vitamin D), keratinization of mucous epithelium (vitamin A), scorbutic lesions (vitamin C), and hemorrhages (vitamin K) (Fig. 13).

It is the same for some mineral deficiencies which influence the blood or the ossification of the bones.

Malformations. Malformations are alterations of morphological development. They can be produced only in young embryos because they are the result of disturbances of the organization period. They are the most spectacular result of some deficiencies.

The most frequently affected is the neural system, but all systems or organs must be concerned. It is noteworthy to know that besides the gross abnormalities there are some histological abnormalities with physiological consequences. They affect principally the neural system and are revealed only by some experimental methods such as maze tests. In humans they are the most important in terms of society.

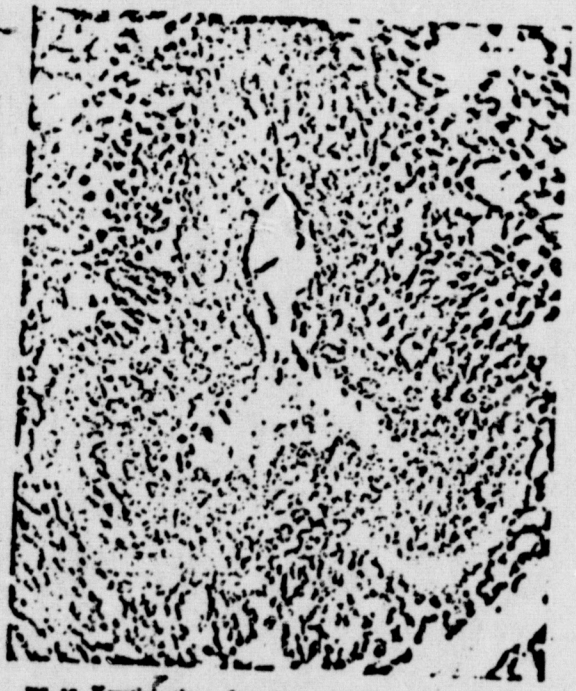

FIG 13. Keratinization of mucous epithelium in vitamin A deficiency. (According to Warkany (329).)

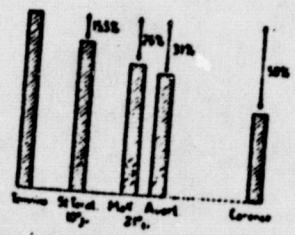

FIG. 14. Mildness of teratogenic pantothenic acid deficiency. At the teratogenic stage the drop in pantothenic acid content in the maternal liver is only 15%. The symptoms of deficiency in the adult appear only when the drop reaches 50%. (According to Giroud et al. (111).)

In nature, these malformations may occur in large areas, and thus they may have great economic importance: such was the case with vitamin A deficiency in pigs or with vitamin E in lambs.

In the laboratory, the frequency of malformations obtained in litters is very variable. Besides abnormal embryos, some may be dead, and others normal in the same litter. Often the frequency is about 30–40%, but under the same conditions only a few embryos may be abnormal; on the other hand the frequency may reach 100%, the variation indicating the complexity of the conditions.

General mildness of teratogenic deficiency. Usually malformations are the result of slight deficiencies.

In the case of vitamin A deficiency, Hale observed (126) that the sows giving birth to abnormal piglets did not themselves present pathological signs. The same occurred in the cow (214). Davis and Madsen (70), by chemical testing, demonstrated that with a content of 16 μg/100 cc in plasma, there are no pathological symptoms in the mother, while levels between 10 and 20 μg/100 cc did not permit normal fetal development. However, in the rat, according to Jackson and Kinsey (149) teratogenic deficiency was rather severe. But perhaps it is not necessary, because Roux et al. (269) have always observed abnormalities by apparently normal mothers.

In teratogenic folic acid deficiency the mothers appear normal. Recently Potier de Courcy (250) confirmed by physiological and chemical testing that this teratogenic deficiency did not modify the maternal organism. In some experiments small alterations in the blood seem to have been noted.

It is perhaps equally true for nicotinic acid deficiency in the chick produced by antagonists.

In pantothenic acid deficiency in the rat, Lefebvres (175) has found that disturbances in embryonic development occur much before pathological symptoms in the mother. The teratogenic action takes place after 14–20 days on a deficient diet, while the first disturbances in the adult are observed only after more than a month (Fig. 14). Giroud et al. (111) have chemically tested the pantothenic acid level in tissues of mothers giving birth to malformed young. At the end of pregnancy on a pantothenic acid-deficient diet, the decrease in pantothenic acid level is only 25%. At the teratogenic stage, i.e., the 10th day, this decrease is still smaller, reaching only 16%.

In teratogenic riboflavin deficiency, the mothers showed no clinical symptoms (102, 329). Giroud et al. (110) have estimated by the vitamin content in the liver of the mother the degree of deficiency which interfered with embryonic development (Fig. 15). At the teratogenic stage, i.e., at the moment the deficiency acts, the decrease is only one-fifth of the normal value (36 μg/g of liver instead of 45 μg).

Thus the chemical data confirm that very small deficiencies may have teratogenic effects.

Types of malformations. The types of malformations are sometimes clearly related to the nature of the deficiency. With vitamin A deficiency the malformations are limited to mesoderm derivatives, not only in the rat but also in other species. This is also the case with riboflavin deficiency obtained by a deficient diet; there are always the same abnormalities: shortening of the limbs with syndactylia and cleft palate.

Nevertheless, as a rule the types of malformations are variable in that they depend on the stage at which the deficiencies act.

Teratogenic stage. In the entire field of teratology the production of malformations is limited to a definite stage of embryonic life: "the teratogenic stage" that corresponds to the organization period of the embryo. During that period the type of malformation varies according to the moment of the organization of each organ; before and after this teratogenic period there is no gross malformation. We observe the same facts in the nutritional deficiencies.

As regards the diet deficient in vitamin A in the sow, Hale (126) noted that malformations are determined

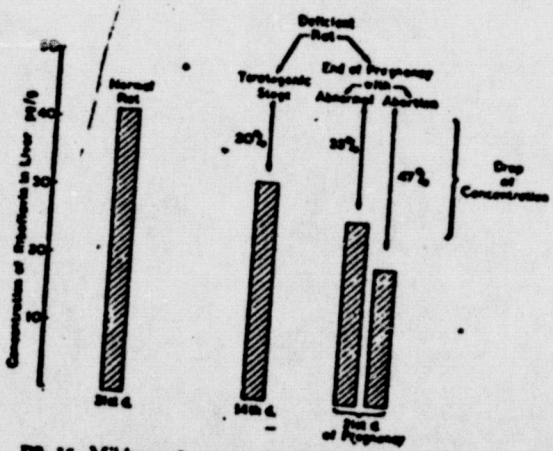

FIG. 15. Mildness of teratogenic riboflavin deficiency produced without antimetabolites. At the teratogenic stage the drop of riboflavin content in the maternal liver is only 20%. (According to Giroud et al. (110).)

before the 30th day; if a supplement of vitamin A is given after this date the litter appears abnormal.

Warkany et al. (327), in the rat deficient in riboflavin, have demonstrated that the period during which the embryo is susceptible to malformations (palate and limbs) is around the 13th day. With a riboflavin deficiency supplemented by an antivitamin (galactoflavin) other anomalies occurred but always from the 7th to the 13th day (221).

With a folic acid deficiency, supplemented by antivitamin (X-methylfolic acid) Evans et al. (83, 84) observed between the 7th and 11th day cerebral and cardiovascular malformations and celosomia, and between the 10th and the 12th day only limb malformations. With aminopterin Baranov (16) noted no damage at the beginning of evolution, a very harmful effect between the 5–13th day, and again no damage in the later stages.

With a niacin antimetabolite Chamberlain and Nelson (49) noted that the maximum teratogenic action occurred on the 5–10th days.

In vitamin E deficiency, which they stopped at definite stages, Thomas and Cheng (304) have observed that teratogenic action is limited to the teratogenic period and its results vary according to the definite stage at which the cessation of deficiency is achieved.

In mineral deficiencies it is the same. In manganese deficiency in the rat, Hurley (141) has seen that the ear defects occurred also in a critical period between the 14th and the 18th day.

INTERACTIONS BETWEEN NUTRITIONAL AND GENETIC CONDITIONS

The physiological behavior of various species is not the same, including the problems of their nutrition. The requirements of mothers and their embryos may also be different.

The hereditary patrimony reveals its important presence in almost all teratological experiments: it must be the same in the nutritional field. It can be assumed that a deficiency which has been proved to be teratogenic in a certain species or strain is not necessarily so in another. In man, this is also true for various individuals because their constitutions are not identical.

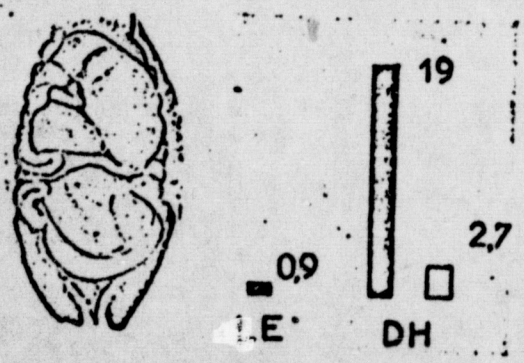

FIG. 16. Interferences between requirements and genetic conditions. Frequency of diaphragmatic hernia in vitamin A deficiency according to the strains of rat. (Modified from Andersen (8).)

FIG. 17. Frequency of open eye by galactoflavin (riboflavin antagonist) in various strains of mice. (Modified from Kalter and Warkany (157).)

Ascorbic acid is synthesized by most animals: their requirements are nil. A few species such as the human, monkey, and guinea pig do not synthesize it, thus it is necessary that it be given to them.

Perhaps for some species nicotinic acid is synthesized from tryptophan and thus it is not necessary for them.

With a diet deficient in vitamin A, Andersen (8) observed 0.9% of diaphragmatic hernias in rats of the Long-Evans strain, and 19% in the strain DH, which has a spontaneous incidence of 2.7% (Fig. 16). This may indicate a special susceptibility to the malformation, such as was the case in some strains of mice treated with cortisone (93). But in other strains of mice there was no such increase in malformations. According to Goldstein et al. (116), the embryos with cleft palate seem more resistant to death by 6-aminonicotinamide than the normal ones (Fig. 17). Kalter and Warkany (157) have also observed very different results in riboflavin deficiency according to the mouse strain: cleft palate, 2.8% in A strain and 41% in DBA, syndactylia, 4.8% in DBA and 82.3% in 129 strain.

Landauer (165) has clearly correlated alterations such as malformations in chick embryos with the various requirements of some strains. Working with Creeper he has demonstrated that rickets in the embryo, from lack of vitamin D, was more severe and easier to obtain than with other strains. Studying the teratogenic action of boron, Landauer (168) saw a disturbance in carbohydrate metabolism, correlated with secondary riboflavin deficiency, which was improved by the addition of riboflavin. Working on various strains of hens, he has seen that malformations were more frequent in the black hens which are known to require more riboflavin than others.

On the other hand, Landauer (170) noted that micro-

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melia and parrot beak produced by 6-aminonicotinamide are similar to genetic chondrodystrophy. He has seen that in chondrodystrophic heterozygotes the teratogenic action of 6-aminonicotinamide is increased, and is on the contrary lessened in animals possessing anti-chondrodystrophy genes. He concludes that 6-amino-nicotinamide has a phenotypic action utilizing the same pathways as the abnormal gene.

Recently Hurley et al. (140, 142) have demonstrated that manganese deficiency in rats, mice, and guinea pigs induces in the offspring an ataxic condition, characterized by incoordination, lack of equilibrium, and associated with defects in vestibular portions of the inner ear. It was a phenocopy of some genetic cases (137) in which three nonallelic genes affect the differentiation of the otoliths of the sacculus and utriculus and cause similar problems of equilibrium. Among the perturbations easy to test there is the inability to swim when the animals are submerged in water. Hurley utilized this test when with Erway and Fraser (80) she studied mice with the pallid gene, of whose offspring 60% are unable to swim. Giving a diet possessing a high manganese content to that strain, she has observed the otoliths may be frequent and that all animals were able to swim, thus correcting a genetic disturbance in metabolism. It was the first complete demonstration where a phenocopy-inducing agent has a reciprocal effect on the mutant itself, correcting the action of the gene. This shows there is a good possibility of finding methods to correct other abnormalities induced by genes.

Recent observations on a botanical compound seem to indicate the possibilities of improving, during gestation and after, the condition produced by the gene of yellow mice. We know that some pregnant mothers may have a high blood level of phenylalanine and that it disturbs her embryo. It may be possible to correct that error as it was done for the phenylketonuric children.

Perhaps by the same methods, it would be possible to correct other abnormal nutritional conditions acting during fetal life.

CONCLUSIONS

All these works demonstrate the importance of many nutrients for the embryo and, for mammals, the necessity of a normal condition of the placenta. They reveal the necessity of a nutritional equilibrium. Some deficiencies or some excesses, or both, may be deleterious: growth stunting, tissular alterations, and malformations. The nutrients coming from the mother's blood depend not only on her feeding but also on her metabolism. This last dependence may have serious repercussions in the case of a metabolic error. According to the progressive growth of the embryo during gestation, its absolute needs increase and feeding of its mother must be improved correlatively. At the present time, the question of nutrition of the embryo is not completely solved. We often need some quantitative values. We recognize also that the problem is complicated by interferences with genetic conditions: it is the reason why the translation of results from one species to another and to humans remains difficult.

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Introduction

I IMAGINE that the main object of Session III is to try to gain some idea of where and how vitamin A is likely to act at the cellular level in the normal animal. This involves a number of complicated issues. For one thing, much of the work on the biological action of this vitamin inevitably concerns the changes produced by either its deficiency or its excess; we have to consider, therefore, how far data obtained under these pathological conditions are relevant to the physiological action of vitamin A. Another difficulty is to determine whether a given cellular effect is primary, secondary, or perhaps occurs even further along a chain of reactions initiated by the vitamin.

In view of the wide variety of scientific disciplines represented at this meeting, I thought that it might help to set the stage for the session, if I briefly recapitulated the basic facts now in our possession about the effects of the vitamin on the living organism.

One of the earliest known functions of vitamin A is in the remodeling of the skeleton. In deficiency, the pattern of bone resorption is disturbed, so that many bones become abnormally thick (1, 2); in the skull and vertebral column, this may have disastrous secondary effects on the nervous system owing to compression of the nervous tissue (3). Excess of vitamin A causes resorption of cartilage and old bone (3); in some animals this may be so extensive as to cause spontaneous fractures. The late Sir Edward Mellanby and I (4) found that a similar effect could be produced by a direct action of retinol on skeletal tissue, since fetal bone and cartilage, when grown in medium containing added vitamin A, underwent rapid and drastic resorption in culture. Hypervitaminosis A does not inhibit the deposition of new bone (3), however, and especially in the cat (5) may cause a severely crippling hyperostosis in many bones.

Another important function of vitamin A, which also was discovered many years ago, is its role in controlling the differentiation of certain epithelia. In deficiency, the secretory epithelia of many organs (6, 7), including those of the respiratory tract and salivary and prostate glands, acquire an epidermoid keratinizing structure. Conversely, the administration of excess vitamin A inhibits the keratinization of some epithelia that normally keratinize (8, 9) and may transform them into a mucus-secreting tissue. This change has been produced in organ cultures of embryonic chicken skin exposed to an excess of vitamin A (10).

In Cambridge, Massachusetts, it is hardly necessary for me to mention the importance of vitamin A in vision; Professor Wald (11) and his colleagues at Harvard University have made a vast contribution to our knowledge of the role of vitamin A in the synthesis of rhodopsin. Without the vitamin, the retina degenerates.

Both hypo- and hypervitaminosis A are teratogenic (12).

Finally, we have the recent discovery by Thompson, Howell and Pitt (13), that vitamin A is essential for the normal functional activity of the reproductive system. Animals can be kept in good general health by the substitution of vitamin A acid for retinol in their diet, but they fail to produce young and become completely blind.

Part I of this session deals with the influence of vitamin A on enzyme activity. It has been shown to affect the synthesis, secretion, and activity of a number of enzymes. Not being a biochemist, I do not

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know as much as I ought about this aspect of the subject and am looking forward to learning more from the four contributors to Part 1.

The only effect on enzymes with which I can claim to be at all familiar is that on lysosomal hydrolases, which my colleagues and I have been studying for some years. In our early work on the effect of vitamin A on tissues grown in organ culture, I grew the explants on a plasma–embryo extract clot. I noticed that those exposed to the vitamin always liquefied the clot much more than their paired controls. Obviously, this suggested that the vitamin had somehow increased the proteolytic activity of the tissue. It occurred to John Dingle that possibly vitamin A was releasing lysosomal enzymes, including the cathepsin, into the intercellular environment. Further work showed his idea to be correct, and it was found that embryonic cartilage (14) and bone (15), grown in organ culture in a fluid medium, released much more lysosomal acid protease into the medium in the presence of vitamin A than did their paired controls. Moreover, the total synthesis of the cathepsin, i.e., the activity released into the medium plus the amount remaining in the explant at the end of the experiment, was also considerably higher in the retinol-treated cultures. The acid protease, which also acts at a neutral pH, though more slowly than at its acid pH optimum, appeared to be largely responsible for the degradation of the cartilage matrix in retinol-treated explants; it was found to digest the protein moiety of the intercellular protein polysaccharide and thus release polymeric chondroitin sulfate ((16) and unpublished results by A. J. Barrett). The role of this enzyme in bone resorption is not yet clear.

Thus, vitamin A has a very broad spectrum of biological effects. One of the questions that I think we ought to discuss, is whether they can all be explained on a unitary hypothesis. My colleagues and I think that this is not impossible.

In Part 2 of this session, we are to hear from Dr. Roels and Dr. Lucy about the action of vitamin A on biological membranes. The first hint that vitamin A might be a membrane-active substance came from a study by John Dingle (17). He was searching for the mechanism whereby the vitamin so greatly increased the extracellular release of lysosomal enzymes from our cartilage explants. He prepared, from rat liver, a subcellular fraction that was rich in lysosomes; to this preparation, vitamin A was added with the result that the bound hydrolases were rapidly released from the lysosomal particles. This effect must be due to structural changes at the molecular level, because when thin sections of the pellet were examined in the electron microscope by Audrey Glauert, although the electron density was slightly reduced, the membranes of the vitamin A-treated lysosomes appeared to be intact (18). Further experiments by Dingle, Lucy, and other members of our Laboratory (for review see 18) demonstrated that the vitamin was hemolytic, caused swelling of isolated mitochondria, and when applied to intact cells altered all their membrane systems, including those of the endoplasmic reticulum and Golgi, and the plasma membrane.

So is it conceivable that the multifarious effects of retinol may prove to be due to the vitamin's membrane-active properties and that the sites of its normal physiological action may be the membrane systems of the cell? I will leave you with this thought to pull to pieces!

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Teratogenic Effects of Hypervitaminosis A in the Hamster and the Guinea Pig

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Teratogenic Effects of Hypervitaminosis A in the Hamster and the Guinea Pig. RENWICK, JANE F. (1970). *Toxicol. Appl. Pharmacol.* 16, 88–99. The teratogenic effects resulting from hypervitaminosis A in the hamster and the guinea pig were studied. Hamsters were treated with 75,000 or 400,000 USP units of vitamin A palmitate per kilogram body weight as single or multiple oral doses during organogenesis. Guinea pigs were treated with 200,000 USP units/kg as a single oral dose during organogenesis. These doses were up to several hundred times the minimum daily requirement of each species. Similar, but not identical, soft tissue and skeletal anomalies, including the following, were produced in each species: exencephaly, brachygnathia, agnathia and other head malformations, shortened, curved legs with impaired or absent ossification at the highest dosage levels, fused ribs, spina bifida, ventricular cleft, and heart and genitourinary system anomalies. The percentage of fetal resorptions and the nature of the anomalies depended on the time of administration and the dose administered. Multiple administration in the hamster at the higher dosage levels produced a higher level of fetal mortality than did any level of single administration. Average fetal weight in the hamster fetuses was decreased by the same dosage level. Fetal growth in the guinea pig was not affected by vitamin A.

The teratogenic effects of hypervitaminosis A in laboratory animals are well documented (Cohlan, 1953, 1954; Deuschle *et al.*, 1959; Kalter and Warkany, 1961; Giroud and Martinet, 1955; Mizutani *et al.*, 1966). Most of these studies were with rats, mice, and rabbits. Few were performed with either guinea pigs (Giroud and Martinet, 1959a,b) or hamsters (Marin-Padilla and Ferm, 1965).

Since previous studies reported anomalies of several body systems, we treated hamsters and guinea pigs on several different days during organogenesis in an attempt to produce the spectra of teratogenic effects of hypervitaminosis A. Our studies confirm and expand the observations reported by Giroud and Martinet (1959a,b) and Marin-Padilla and Ferm (1965).

METHODS AND MATERIALS

Golden Syrian hamsters, *Mesocricetus auratus*, and Coulson strain guinea pigs, *Cavia porcellus*, were used. The hamsters were shipped to our laboratories by the commercial supplier the second day after breeding. The guinea pigs were mated in our laboratory. The first day after mating was considered as day 0 of gestation.

Vitamin A was administered as individual oral doses during the period of organogenesis. A water-dispersible vitamin A palmitate,[2] 250,000 USP units/g, was suspended in distilled water. The various concentrations were prepared to give a uniform dose volume of 1 ml/100 g body weight. Control animals received vehicle by intubation.

In the hamster, single administration was on day 7, 8, 9, or 10 of gestation; multiple administration was from days 6 through 10. On each of days 14 through 20 of gestation, different groups of guinea pigs were given single doses.

On day 15 of pregnancy, the hamsters were killed with carbon dioxide. The uterus was opened and examined for the presence of resorption sites; the fetuses were removed, weighed, and examined for external malformations. The viability of the living fetuses was checked by placing them in a shallow hatching incubator for 6 hours. Most guinea pigs were allowed to deliver normally since they do not cannibalize their young. A few were sacrificed at 50 days of gestation. All pups were weighed at birth and examined for external malformations. In addition, fetuses showing gross abnormalities were examined further for bone defects by fixation in alcohol, clearing, and staining in Alizarin red and for internal malformations with the aid of a dissecting microscope when necessary.

Both fetuses dying in late embryonic life and resorption sites were counted as dead fetuses. This number as a fraction of the total number of implantation sites is the percent fetal mortality. The percentage of terata was based on the total number of fetuses in which abnormalities could be recognized, that is, both living and dead fetuses.

Average fetal weight for the hamster fetuses was calculated by totaling litter weights and dividing by the total number of fetuses. Newborn guinea pigs were weighed individually, and the weights were averaged. Average individual fetal weights rather than litter weights are reported since the former generally reflect more accurately the size and condition of the fetuses. Total weight varies more as a function of the number of fetuses than of their individual size.

RESULTS

Hamsters

Tables 1 and 2 summarize the results of vitamin A administration to the hamsters.

Head anomalies were common as a result of maternal treatment on day 7. The pale fetuses often had severe exencephaly. Others had lesser degrees of the same anomaly; in a few the exencephaly was so slight that only a cutaneous pimple in the center of the cranium could be seen on gross examination. Microcephaly, a shortening of the premaxillae, maxillae, and/or mandibles, and a few cases of hydrocephalus are included in the category of malformed heads. At 400,000 USP units/kg, severe shortening of the jaws occurred, particularly of the lower jaw (agnathia). Maxillomandibular anklyosis was present in these fetuses, and the oral opening was small or nonexistent. Lower doses generally produced greater shortening of the upper jaw than of the lower jaw (Fig. 1).

Associated with the arrested development of the head, the orbital cavity was shallow. Many fetuses had unilateral or bilateral bulging eyes not covered by lids (exophthalmos), and in a few cases, the eyes were small or absent.

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TABLE 1

EFFECTS OF HYPERVITAMINOSIS A ON FETAL DEVELOPMENT IN THE HAMSTER

Day of gestation treated	Dose by oral intubation (USP units/kg)	No. of mothers	Live fetuses: Total	Live fetuses: Per litter	No. dead fetuses at term	No. resorption sites	Fetal mortality (%)	Av. fetal weight (g)	% of fetuses dead in 6 hr	Teratomas: No.	Teratomas: %
7	400,000	5	36	7.2	5	6	23.4	1.8	100	41	100
7	200,000	17	139	8.2	14	32	34.9	2.0	63.3	123	88.4
7	150,000	4	38	9.5	9	4	25.5	2.1	76.5	29	61.5
7	100,000	5	55	11.0	—	—	—	2.2	7.3	14	25.5
7	75,000	4	50	12.5	—	2	3.8	2.3	4.0	0	—
8	400,000	7	65	9.3	—	15	19.8	2.1	67.7	65	100
8	300,000	5	47	9.4	1	6	13.0	2.0	74.5	47	100
8	200,000	23	248	19.8	—	17	9.7	2.0	33.5	196	79.0
8	100,000	3	32	10.7	—	—	—	2.3	—	0	—
9	400,000	13	137	10.5	1	7	5.5	2.1	31.4	91	66.9
9	200,000	13	138	10.6	2	2	2.9	2.2	1.5	73	52.1
9	100,000	3	31	10.3	—	—	—	2.3	—	0	—
10	400,000	5	48	9.6	—	5	9.4	2.1	6.3	48	100
6–10	400,000/day	3	—	—	—	32	100	—	—	0	—
6–10	200,000/day	8	42	5.3	—	54	56.3	1.9	83.3	32	76.2
6–10	150,000/day	5	45	9.0	2	8	18.2	2.0	62.2	29	64.7
6–10	100,000/day	8	78	9.8	3	4	8.2	2.2	5.1	6	7.6
6–10	75,000/day	5	57	11.4	1	—	1.7	2.1	10.5	3	5.2
Controls		99	1081	10.9	3	29	2.9	2.3	0.6	4	0.4

TABLE 2

SPECIFIC FETAL ANOMALIES ASSOCIATED WITH HYPERVITAMINOSIS A IN THE HAMSTER

Day of gestation treated	Dose by oral intubation (USP units/kg)	No. of mothers	No. malformed/total No. fetuses	Exencephaly	Malformed heads	Bulging eyes	Cleft palate	Spina bifida	Fused ribs	Short tail	Leg anomalies	Umbilical hernia
7	400,000	5	41/41	8	36	41	—	16	16	30	—	1
7	200,000	17	123/153	16	63	61	2	10	38	1	—	2
7	150,000	4	29/47	11	7	8	2	1	17	—	—	1
7	100,000	5	14/55	—	12	5	—	—	—	—	—	—
7	75,000	4	0/50	—	—	—	—	—	—	—	—	—
8	400,000	7	65/65	—	5	2	—	1	—	65	1	3
8	300,000	5	47/48	—	3	5	10	—	—	47	—	2
8	200,000	23	196/248	—	7	8	4	1	1	188	—	2
8	100,000	3	0/32	—	—	—	—	—	—	—	—	—
9	400,000	13	91/138	—	—	—	—	—	21	2	89	—
9	200,000	13	73/140	—	1	—	4	—	—	—	71	—
9	100,000	3	0/31	—	—	—	—	—	—	—	—	—
10	400,000	5	48/48	—	3	—	5	—	—	—	48	—
6–10	400,000/day	3	0/0	—	—	—	—	—	—	—	—	—
6–10	200,000/day	8	32/42	—	3	26	14	1	30	—	—	—
6–10	150,000/day	5	29/47	—	4	1	2	—	26	—	—	—
6–10	100,000/day	8	6/81	—	—	—	—	—	5	—	—	—
6–10	75,000/day	5	3/58	—	—	—	1	1	1	—	—	—
Controls		99	4/1081	1	1	—	—	—	1	—	—	1

FIG. 1. Hamsters. Alizarin red stain. Top fetus: Maternal treatment (oral intubation) with vitamin A (200,000 USP units/kg body weight) on day 7 of gestation, resulting in shortened maxillae and mandibles. Lower fetus: Control.

Malformations from treatment on day 7 occurred from doses as low as 100,000 USP units/kg. None appeared in the litters of the 4 animals treated at 75,000 USP units/kg.

A high percentage of fetuses had short or curved tails as a result of treatment at 200,000–400,000 USP units/kg on day 8. The highest dose on day 7, 400,000 USP units/kg, but not the lower doses, also caused shortened tails. When radiographed or stained with Alizarin red, these fetuses with shortened tails had irregular lumbar, sacral, and or coccygeal vertebrae. Examination of internal organs showed that the kidneys were often small, absent, or hydronephrotic. Several fetuses had imperforate anus; one at the highest treatment level had an ectopic heart.

Treatment on day 9 produced a high percentage of leg defects (Figs. 2 and 3). These included short, thickened legs (micromelia), fused and missing toes (ectrodactylia), and abnormal flexion of joints (arthrogryposis). The most severely affected animals lacked any calcification centers in either the fore or hind limb. All limb anomalies are reported together in Table 2. As at day 8, a level of 200,000 USP units/kg produced anomalies but 100,000 USP units/kg did not.

Leg anomalies from treatment on day 10 were confined to shortened feet and toes except for 6 fetuses which also had arthrogryposis in one or more legs.

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FIG. 2. Hamsters. Right fetus: Maternal treatment on day 9 of gestation, resulting in small size, micromelia, and arthrogryposis. Left fetus: Control.

FIG. 3. Feet of hamsters. Left: Maternal treatment on day 9 of gestation, resulting in short, thick legs and micromelia; no calcification when radiographed. Right: Control.

At the highest single dose, 400,000 USP units/kg, most of the fetuses from treatment at any given day were extremely malformed and small and did not survive for the 6-hour period. Usually these fetuses and those from other levels and days of administration which died in the incubator did so within the first hour. When they were examined internally with the aid of a dissecting microscope, heart and great vessel anomalies were found; these included underdevelopment of the left auricle and ventricle, and truncus arteriosis in the most severe cases. Several fetuses were stillborn from mothers dosed on day 7. No respiratory movements could be elicited, although from their condition they apparently had not been dead *in utero*. In most cases they were extremely pale and often edematous.

Litters from mothers treated 5 times (days 6–10) had a large percentage of resorptions. Those fetuses living until term had a wide variety of both external and internal defects but did not have leg anomalies. Many of those treated at 150,000 or 200,000 USP units/kg/day died in the incubator and had heart anomalies. Few terata resulted from treatment with 75,000 or 100,000 USP units/kg/day.

Guinea Pigs

Table 3 shows the results of vitamin A administration to guinea pigs. Litters sacrificed at 50 days of gestation were similar to those delivered at term but, to simplify tabulation of data, are not included; however, results are discussed when applicable.

TABLE 3

EFFECTS OF HYPERVITAMINOSIS A ON FETAL DEVELOPMENT IN THE GUINEA PIG (ORAL ADMINISTRATION)[a]

Day of treatment	No. of litters	No. malformed/ total No. fetuses	Av. fetal weight	Anomalies found
14	4	11/13	95.8	Agnathia, crooked incisors, malformed pinna, ataxia, hypoplastic tympanic bullae, microcephaly
15	7	21/28	95.0	Agnathia, crooked incisors, malformed pinna, hypoplastic tympanic bullae, uterus unicornis, microcephaly, ataxia, atresia ani
16	8	13/33	83.7	Short tails, shallow thoracic cavity, malformed pinna, hyperdontia, microcephaly, agnathia, synotia, ataxia
17	6	10/26	85.3	Short tails (missing coccygeal vertebrae), agnathia
18	3	2/16	95.0	Arthrogryposis hind legs—shortened crooked tibiae and fibula
19	3	3/14	96.4	Short bowed front legs, dichiria and syndactylia of front toes
20	4	9/13	89.6	Short and bowed front and hind legs
Controls	39	1/226	88.9	Conjoined twins

[a] Treatment in all cases was 200,000 USP units/kg.

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Most pups from mothers treated on day 14 had microcephaly, micrognathia, or even agnathia (Figs. 4 and 5). Their upper molars were long and malpositioned. The animals which were less seriously affected had both upper and lower incisors, but these teeth were also malpositioned, and all had macrostomia. Radiographs of the head showed unilateral or bilateral hypoplastic or absent tympanic bullae. The severely affected animals were all stillborn; one with an apparently normal head was ataxic.

The external ears or pinnae of some pups were small and/or notched in the outer margin, rather than being round and full as in the normal guinea pig. This anomaly was

FIG. 4. Heads of guinea pigs, stained with Alizarin red. Top: Maternal treatment on day 15 of gestation, resulting in micrognathia, malpositioned incisors, and elongated and narrow head. Bottom: Control.

present in stillborn animals as well as in some which were apparently otherwise normal at birth. In some litters sacrificed at 50 days of gestation, fetuses had open eyes. Normally the eyes are still closed at this time. The head anomalies resulting from administration on day 15 were generally similar to those from day 14. In addition, one animal had uterus unicornis; another had atresia ani with the urogenital tract also ending blindly.

Following administration on day 16, fewer pups had agnathia; however, one had synotia combined with agnathia. The larynx and pharynx opened to the exterior on the ventral side of the neck between the ears. One fetus had hyperdontia (a third lower incisor), and 2 others with short tails had missing coccygeal vertebrae.

After treatment on day 17, some of the same defects were present; 7 fetuses from one litter had agnathia, and 3 in another had short tails. Their shortened tails were not associated with atresia ani as with some of the hamsters; thus viability was not

affected and the animals grew normally. A fetus from a litter sacrificed at 50 days had a missing left kidney and a heart anomaly.

FIG. 5a. Radiograph of guinea pig head. Maternal treatment on day 19, resulting in agnathia and absence of tympanic bullae.

FIG. 5b. Radiograph of head of control guinea pig.

Two pups from administration on day 18 had shortened, bowed tibias and fibulas and arthrogryposis of the tarsal joint. Another sacrificed at 50 days had an extremely hypoplastic left ovary and uterus.

As a result of treatment on day 19, 3 pups from one litter had thickening and bowing of the radius and ulna (Fig. 6). Two animals in another litter had fusion of digits 3 and 4 of the front feet (syndactyly). Dichotomy or partial duplication of digit 2 was also present in one foot.

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Following treatment on day 20, all fetuses in 2 litters had shortening and bowing of the radius and ulna; in 2 other litters the tibia and fibula were shortened and the tarsal joint twisted.

Fetal growth was not affected by vitamin A. The average fetal weights at birth for the 130 fetuses in the 39 treated litters and that of the 226 fetuses in the 59 control litters were both 89 g.

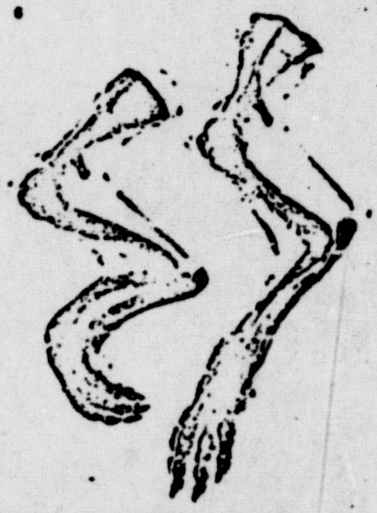

FIG. 6. Guinea pig forelimbs stained with Alizarin red. Left: Maternal treatment on day 20 of gestation, resulting in shortening and bowing of radius and ulna. Right: Control.

DISCUSSION

The times of administration in both the hamster and the guinea pig were chosen to coincide with the most critical period in organogenesis. Days 7, 8, or 9 were chosen for single, and 6 through 10 for multiple, administration in the hamster since implantation in the hamster is completed on day 5 and the most rapid period of organogenesis is 7 8.5 days (Boyer, 1948). Days 14–20 were chosen for treatment in the guinea pig to coincide with days of comparable organogenesis in the hamster (Scott, 1937).

A wide variety of visceral and skeletal abnormalities were produced in both species. Cranial anomalies and shortened maxillae were common in the hamster but were not found in the guinea pig. Agnathia, however, was much more pronounced in the

guinea pig. Hamster development at term was not complete enough to demonstrate possible effects on the tympanic bullae. Extreme micromelia was produced in the hamster, but only at doses higher than those used in the guinea pig.

The incidence of fetal death in the hamster was dependent upon both developmental stage and dose administered. Fetal death and resorption were high in the hamster after administration at day 7, at the highest level of administration, on day 8, and after multiple administration (days 6–10). The incidence of fetal death in the guinea pigs is not known since a sufficient number of mothers were not sacrificed for examination of the uterus and ovaries for resorption sites and number of corpora lutea. It is not likely that vitamin A caused fetal death in the guinea pig litters carried to term since treated litters averaged 3.6 fetuses per litter and the controls averaged 3.8 fetuses per litter. However, vitamin A may have caused early fetal death. Some of the days of treatment occurred before normal estrous recycling, and even a presumptive diagnosis of pregnancy could not be made at this time. Lethality to all the embryos could have been determined only by sacrificing the mothers soon after treatment or by comparing pregnancy rates in a large number of treated and control guinea pigs.

These studies demonstrate (in contrast to Marin-Padilla and Ferm, 1965) that additional abnormalities in hamsters can be produced and recognized, both by using higher doses and by using more methods of examination of fully developed term hamster fetuses. Extremely retarded limb and tail development, imperforate anus, hydrencephalus and anencephalus, and a comparison of fetal viability were not reported previously.

Giroud and Martinet (1959a,b) treated their guinea pigs on days 12–14 of gestation and reported a large number of abortions or resorptions, in addition to lesions of the mandible and hyoid tongue. The present studies with administration slightly later in gestation demonstrated more severe mandibular abnormalities, synotia, small or absent tympanic bullae, and limb abnormalities. Although it was not the purpose of this study to establish a minimum teratogenic level of vitamin A, some comparison of the doses used and the effects which resulted with that of the vitamin A requirement is of interest. A satisfactory level of vitamin A to meet the nutritional requirements of the hamster is reported as 1300 IU/100 g of diet (NAS–NRC, 1962). If we assume that the hamster consumes 10 g of food per day, his daily requirement is 130 IU (1300 IU/kg of the body weight is 100 g). The dose of 75,000 USP units/kg for 5 days is probably near the minimum teratogenic dose for the hamster. This is 60 times the daily requirement, and the dose of 300,000 USP units needed to produce severe anomalies is 150–160 times the daily requirement.

Bentley and Morgan (1945) stated that the vitamin A requirement of the guinea pig was 2 mg/kg of body weight when fish liver oil was the source of the vitamin. Gal *et al.* (1968) stated that the minimum requirement was 0.2 mg of vitamin A per animal on the basis of 20 g of feed consumed daily. Since the latter study used crystalline retinyl palmitate as a source of vitamin A, we can assume that the requirement was 360 IU per animal daily. If we further take 500 g as an average weight for their animals, then the requirement is 720 IU/kg. Anomalies in guinea pigs were produced in this study with a dose of 200,000 IU/kg or nearly 300 times the daily requirement.

The method of action of hypervitaminosis A in producing teratogenesis is not known. Direct action of vitamin A on the fetus, excessive production of adrenocortical

hormones, and fall in blood concentration of thyroid hormone have been considered (Takeuchi, 1964). Keehhar (1968) believed that at least the cephalic malformations caused by vitamin A occurred from disrupted inductive relation between epithelium and mesoderm. In his studies of rat embryos treated on days 10, 11, and 12 of gestation, decreased rates of thymidine-^{3}H uptake inhibited cell proliferation in liver, some cephalic areas, skin, and the trigeminal nucleus.

On the cellular level, vitamin A may effect change by participating in cellular metabolism, or the adverse effects may be caused by physical characteristics of the vitamin on the developing cells. Lucy (1964) stated that excessive vitamin A *in vitro* on embryonic chick limb bone rudiments changed membrane permeability by affecting the lipoprotein membrane of cell organelles.

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FEATURES PECULIAR TO TRANSPLACENTAL TRANSITION OF SEMISYNTHETIC PENICILLIN — OXACILLIN

A. P. Kiryuchenkov, S. D. Voropaeva, V. G. Kurdyukova

The transplacental passage of oxacillin was studied in clinical and experimental conditions. In single intramuscular injection of 500 mg of the preparation to parturients its content in the fetal blood during the first hour after administration was several times lesser than in the maternal blood. 3 and 6 hours after injection of the antibiotic its level in the fetal blood did not essentially differ from that in the maternal blood. During the whole period of investigation (6 hours) the content of oxacillin corresponded to the minimal bacteriostatic effect in respect to most strains of staphylococci. In experiments the authors studied the peculiarities of transplacental passage in the stage of placentation (13th day of pregnancy) and the state of formation of a mature placenta (20th day of pregnancy). At the end of pregnancy the permeability of the placenta to oxacillin [illegible]

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● ШИРОТА ТЕРАТОГЕННОГ
ПРИМЕНЕНИЯ ЛЕКАРСТ

В. Б. Прозоровский, В:

Центральная научно-исследо
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Проблеме врожденных порс
все большее внимание. Тератоге
посвящены многочисленные раб
лаков и М. А. Репина; Karnofsky

Опыты на животных помогак
ставлять опасность также и для
непосредственно, очевидно, что к вещ
нами в эксперименте, нужно
клинике. Однако до настоящего в
рым степень тератогенности пре
тивно.

В данной работе в качестве
венного препарата во время бр
тератогенного действия (широта
отношение максимальной тератог
мальной тератогенной дозой подра
рой беременным животным возн
при минимальном количестве рез
зуемается такая доза, при введен
шению нормального потомства с п
скопических, физиологических, био
ния можно установить минимальны

няющиеся в течение всей жизни животного отличия от нормальных животных. Эти отличия свидетельствуют о возникновении скрытого органического, функционального или биохимического порока.

С целью воспроизведения у крысят функционального порока мозга, проявляющегося в нарушении поведения, испытывали тератогенное действие мielосана, хлоридина и витамина А, т. е. тех препаратов, при введении которых, согласно литературным данным (Jackson; A. O. Натансон; Е. А. Пожидаев; А. М. Черпух и П. Н. Александров, и др.), уродства мозга встречаются наиболее часто. Для того чтобы пороки развития мозга не осложнялись возникновением пороков развития других органов, препараты вводили крысам на 9-й день беременности, что соответствует критическому периоду развития мозга крысят (Hamburger). Этот день избран также и потому, что, по данным А. М. Черпуха и П. Н. Александрова, а также А. П. Дыбана, именно на него приходится максимальная тератогенная активность мielосана и хлоридина. Средние смертельные дозы препаратов определяли на взрослых интактных крысах (самках) по методу, предложенному В. Б. Прозоровским.

Так же, как и в опытах других авторов, масляные растворы мielосана и хлоридина вводили внутрибрюшинно, а витамина А — в желудок. При определении максимальной тератогенной дозы крыс, получивших тератоген, на 18-й день беременности забивали и плоды извлекали. [illegible] каждой данной дозы [illegible] бировали таблицу) цефалия, при еди ций резко ным дру-

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FEATURES PECULIAR TO TRANSPLACENTAL TRANSITION OF SEMISYNTHETIC PENICILLIN — OXACILLIN

A. P. Kirpichnikov, S. D. Veroperova, V. G. Kurdyukova

The transplacental passage of oxacillin was studied in clinical and experimental conditions. In single intramuscular injection of 500 mg of the preparation to parturients its content in the fetal blood during the first hour after administration was several times lesser than in the maternal blood 3 and 6 hours after injection of the antibiotic its level in the fetal blood did not essentially differ from that in the maternal blood. During the whole period of investigation (6 hours) the content of oxacillin corresponded to the minimal bacteriostatic effect in respect to most strains of staphylococci. In experiments the authors studied the peculiarities of transplacental passage in the stage of placentation (13th day of pregnancy) and the state of formation of a mature placenta (20th day of pregnancy). At the end of pregnancy the permeability of the placenta to oxacillin decreased somewhat.

УДК 618.035:617.3

ШИРОТА ТЕРАТОГЕННОГО ДЕЙСТВИЯ КАК ПОКАЗАТЕЛЬ ОПАСНОСТИ ПРИМЕНЕНИЯ ЛЕКАРСТВЕННОГО ВЕЩЕСТВА ВО ВРЕМЯ БЕРЕМЕННОСТИ

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Проблеме врожденных пороков развития с каждым годом уделяется все большее внимание. Тератогенному действию лекарственных препаратов посвящены многочисленные работы (В. И. Бодяжина; М. А. Петров-Маслаков и М. А. Репина; Karnofsky; Tuchmann-Duplessis; Yaffe, и др.).

Опыты на животных помогают выявить препараты, которые могут представлять опасность также и для человека. Хотя механический перенос доз допустим, очевидно, что к веществам оказавшимся активными тератогенами в эксперименте, нужно относиться с большой осторожностью и в клинике. Однако до настоящего времени нет надежных критериев, по которым степень тератогенности препарата можно было бы оценить объективно.

В данной работе в качестве показателя опасности применения лекарственного препарата во время беременности рекомендуется индекс широты тератогенного действия (широта тератогенного действия), вычисляемой как отношение максимальной тератогенной дозы к минимальной. Под максимальной тератогенной дозой подразумевается такая доза, при введении которой беременным животным возникает максимальное количество уродств при минимальном количестве резорбций плодов. Под минимальной подразумевается такая доза, при введении которой у родившегося внешне совершенно нормального потомства с помощью специальных электронномикроскопических, физиологических, биохимических и других методов исследования можно установить минимальные, но статистически достоверные и сохраняющиеся в течение всей жизни животного отличия от нормальных животных. Эти отличия свидетельствуют о возникновении скрытого органического, функционального или биохимического порока.

С целью воспроизведения у крысят функционального порока мозга, проявляющегося в нарушении поведения, испытывали тератогенное действие мielосана, хлоридина и витамина А, т. е. тех препаратов, при введении которых, согласно литературным данным (Jackson; А. О. Натансон; Е. А. Пожидаев; А. М. Чернух и П. Н. Александров, и др.), уродства мозга встречаются наиболее часто. Для того чтобы пороки развития мозга не осложнялись возникновением пороков развития других органов, препараты вводили крысам на 9-й день беременности, что соответствует критическому периоду развития мозга крысят (Hamburger). Этот день избран также и потому, что, по данным А. М. Чернуха и П. Н. Александрова, а также А. П. Дыбана, именно на него приходится максимальная тератогенная активность мielосана и хлоридина. Средние смертельные дозы препаратов определяли на взрослых интактных крысах (самках) по методу, предложенному В. Б. Прозоровским.

Так же, как и в опытах других авторов, маслянные растворы мielосана и хлоридина вводили внутрибрюшинно, а витамина А — в желудок. При определении максимальной тератогенной дозы крыс, получивших тератоген, на 18-й день беременности забивали и плоды извлекали. При введении каждой данной дозы подсчитывали число уродливых и число резорбированных плодов. При введении максимальных тератогенных доз (см. таблицу) число плодов с выраженными морфологическими уродствами (анэнцефалия, мозговая грыжа, общее недоразвитие и т. п.) достигало 30—40% при единичных случаях гибели. При введении больших доз число резорбций резко возрастало. Полученные результаты полностью соответствуют данным других авторов.

Летальные и тератогенные дозы и показатели тератогенности витамина А, хлоридина и мielосана для крыс

Доза и показатель	Витамин А (в МЕ)	Хлоридин (в мг/кг)	Мielосан (в мг/кг)
$ЛД_{50}$ для самок	600 000	40	50
Тератогенная доза максимальная	300 000	8	5
минимальная	60 000	0.8	0,05
Терапевтический индекс	2	5	10
Широта тератогенного действия	5	10	100

С целью определения минимальных тератогенных доз выращивали потомство крыс, получивших препараты в дозах, намного меньших, чем максимальная тератогенная. По среднему числу крысят в помете, по их внешнему виду, весу мозга и его частей, а также по срокам прозревания эти крысята не отличались от контрольных, родившихся от самок, получавших одно персиковое масло. По достижении теми и другими крысятами месячного возраста сопоставляли их поведенческие реакции. Определяли чувствительность нарушения поведения от величины дозы антенатального воздействия.

Двигательную активность оценивали с помощью специально сконструированного прибора (В. Г. Малаховский) путем регистрации числа замыканий пластин пола при каждом шаге животного в течение 10 мин. после 50-минутной адаптации.

Скорость выработки оборонительных условных рефлексов определяли в камере, разделенной на два отсека. При подаче тока в 10 *в* на пол крыса перепрыгивала через перегородку. Условным раздражителем служила лампа

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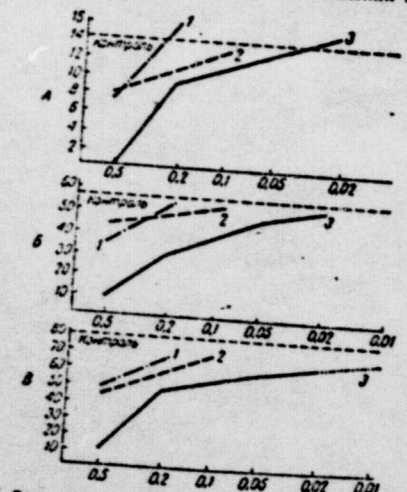
белого цвета. Скорость выработки условного рефлекса рассматривали как величину, обратную числу сочетаний, необходимому для возникновения первой условнорефлекторной реакции.

Способность к правильному выбору пути избегания изучали в камере оригинальной конструкции (В. Г. Малаховский), состоящей из двух этажей. Определяли скорость ухода крыс с пола нижнего этажа по вертикальному столбу через отверстие в полу верхнего этажа. Скорость вычислена как величина, обратная времени с момента подачи тока на пол нижнего этажа и до прихода на верхний этаж.

Приведенные на рисунке результаты не оставляют сомнений, что наиболее выраженные изменения поведения при дозе, равной 0,5 максимальной тератогенной, вызывал миелосан. Далее следует витамин А и хлоридин. Кривая зависимости величины обнаруживаемого эффекта от введенной дозы наиболее крута у витамина А. Тератогенный эффект миелосана не исчезает даже при многократном уменьшении дозы, а эффект витамина А становится ничтожным уже при снижении дозы в 5 раз. Наиболее чувствительным из испытанных методов оценки поведения оказался «выбор пути избегания»; именно по результатам этой серии опытов определяли минимальную тератогенную дозу. Для витамина А она в 5 раз, а для хлоридина в 10 раз меньше максимальной тератогенной. Для миелосана же даже в 50 раз меньшая доза не является достаточно малой. При самой точной экстраполяции она составляет $^1/_{100}$ от максимальной тератогенной. Эти дозы в их абсолютном значении, а также их соотношение приведены в таблице.



Зависимость показателей поведения крыс от дозы тератогенных агентов.

1 — витамин А; 2 — хлоридин; 3 — миелосан. По оси абсцисс: относительная величина тератогенной дозы (за 1 принята максимальная тератогенная доза каждого вещества); по оси ординат: А — число ошибок выработки условнорефлекторной реакции торможения; Б — скорость выработки условнорефлекторной реакции (оборонительные условные рефлексы); В — скорость ухода крыс с нижнего пола камеры (реакция выбора пути избегания).

По мнению Robson, показателем опасности применения препарата может служить «терапевтический индекс» — отношение дозы, токсической для матери, к дозе, вызывающей уродство плодов. Очевидно, что при такой оценке опасность использования витамина А, хлоридина и миелосана относится как 1:2,5:5. Согласно же индексу широты тератогенного действия, относительная тератогенность препаратов составляет 1:2:20. Миелосан в 20 раз, а хлоридин в 2 раза опаснее витамина А.

Установленные в результате исследования минимальные тератогенные дозы, естественно, являются минимальными только при введении препаратов в данный день и при данных методах выявления тератогенного эффекта. Не исключена возможность, что при введении препаратов в иные сроки или при изучении тератогенного воздействия на клеточном и молекулярном уровнях эти дозы в дальнейшем могут оказаться меньшими. Однако практическая невозможность охватить в одном исследовании все органические, функциональные и биохимические сдвиги не делает найденные дозы ошибочными.

Она означает лишь, что минимальные тератогенные дозы, так же как и другие показатели, выявленные на основании определения начальных, пороговых поражений (терапевтическая широта, предельно допустимые дозы и т. п.) по мере совершенствования техники эксперимента будут уточняться. Весьма существенно отметить, что сделанные на основании проведенного исследования выводы согласуются с результатами клинических наблюдений, согласно которым, применение миелосана в терапевтических дозах у беременных женщин приводит к возникновению уродств у новорожденных (Bollag; Jackson; Diamond и Anderson), в то время как возникновения уродств в результате приема витамина А у человека не отмечено (А. П. Дыбан). Наиболее существенным является оценка тератогенности хлоридина; широко применяемого в акушерстве для лечения токсоплазмоза. Учитывая малую широту его тератогенного действия, можно предполагать, что применение препарата в клинике не должно вести к возникновению аномалий развития центральной нервной системы. Это предположение подтверждается тем, что в обзорах по клинической тератологии хлоридин как тератоген не упоминается (А. П. Кирющенков и Б. В. Леонов; Pontuch).

Очевидно, обсуждаемые показатели (терапевтический индекс и широта тератогенного действия) не заменяют и не исключают друг друга. Терапевтический индекс позволяет оценить сравнительную опасность препарата для матери и плода при применении больших, токсических доз. Тератологическая широта характеризует скорее сам препарат и позволяет оценить опасность его применения в дозах, намного ниже токсических. Мы полагаем, что для клинициста тератологическая широта явится более подходящим показателем для выбора своего отношения к препарату.

Выводы

1. Введение беременным самкам крыс тератогенных веществ в дозах, не вызывающих видимых уродств плода, может приводить к появлению у него функциональных пороков.

2. Степень опасности использования препарата во время беременности с точки зрения возникновения у плода функциональных пороков может быть оценена на основании индекса широты тератогенного действия.

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THE RANGE OF TERATOGENIC ACTION AS AN INDEX OF THE HAZARD OF USING A MEDICINAL SUBSTANCE DURING PREGNANCY

V. B. Prozorovsky, V. G. Malukhovsky

In experiments on rats the authors determined the teratogenic doses of myelosan, chloridine and vitamin A for fetuses during the introduction of these substances to females on the 9th day of pregnancy. As maximally teratogenic was a dose which caused monstrosities

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in 30—40 per cent of fetuses. As minimally teratogenic the authors accepted a dose which in a normally born one-month-old progeny caused behavior deviations in comparison with control animals. The authors propose to characterize the degree of teratogenicity of drugs and the hazard of their clinical employment by the range of teratogenic action, which is determined by the ratio between the maximal and minimal teratogenic dose.

УДК 618.36+618.7-085.1-085.256.84-089.71

ПРИМЕНЕНИЕ МЕТИЛЭРГОМЕТРИНА У РОЖЕНИЦ, УГРОЖАЕМЫХ ПО КРОВОТЕЧЕНИЮ

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В настоящем исследовании изучали клиническую эффективность метилэргометрина, примененного с профилактической целью у рожениц, угрожаемых по кровотечению (отягощенный акушерский анамнез, перерастяжение матки, поздние токсикозы, заболевания сердечно-сосудистой системы).

Кроме того, было проведено комплексное изучение влияния метилэргометрина на организм родильницы, в частности на функциональную способность миокарда, свертывающую систему крови, сократительную способность матки, кровенаполнение и тонус ее сосудов.

С этой целью был проведен клинический анализ течения последового и раннего послеродового периода после медикаментозной профилактики у 1025 родильниц, угрожаемых по кровотечению. Контрольную группу составили 498 родильниц, которым профилактика не проводилась (архивный материал 1963—1965 гг.).

Действие препарата на организм родильницы изучали с помощью методов поликардиографии, электрогистерографии, реогистерографии. Кроме того, оценка состояния свертывающей системы крови проводилась на основании анализа коагулограмм и тромбоэластограмм.

Метилэргометрин применяли внутривенно в количестве 0,1—0,2 *мг* вещества вместе с 5 *мл* 40% раствора глюкозы или физиологического раствора при прорезывании головки, переднего плечика или сразу же после рождения плода.

Метилэргометрин был использован у рожениц в возрасте от 20 до 44 лет. При этом 37,5% женщин были первобеременными, 23,4% — повторнобеременными первородящими и 39,1% — повторнородящими. В контрольной группе первобеременных было 31,7%, повторнобеременных первородящих — 23,5%, повторнородящих — 44,8%.

Предшествующая беременность закончилась абортами у 38,4% женщин в группе первородящих и у 83,2% в группе повторнородящих (в контрольной группе соответственно 40,2 и 77,1%). У 45,8% рожениц предыдущие роды были патологическими. В контрольной группе осложненное течение предыдущих родов было у 31,4% женщин.

Самостоятельное отделение последа произошло у 97,4% женщин (в контроле у 91,4%). Среднее время отделения последа составило в группе первородящих 8 мин. 13 сек. ±0,02, а у повторнородящих 8 мин. ±0,04 (в контроле соответственно 12 мин. ±0,05 и 14 мин. ±0,01).

Операция ручного отделения последа в исследуемой группе проведена у 2,6% рожениц, в контрольной группе — у 8,6%. У 17 женщин основной группы показанием к ручному отделению последа явилось плотное его прикрепление, у 10 — начавшееся кровотечение. В контрольной группе у большинства родильниц (38 из 43) показанием к этой операции было кровотечение, а у 6 — плотное прикрепление.

Операция ручного обследования стенок полости матки в группе с применением метилэргометрина была произведена у 4,3% (в контроле у 17%). Показаниями к ручному обследованию полости матки были: кровотечения — 1,4% (контроль 11,6%), дефект последа — 1,2% (контроль 2,6%), сомнение в целости плаценты — 0,8% (в контроле 1,6%). Ущемление последа произошло у 0,4% женщин, а в контрольной группе — у 0,8%.

Применение метилэргометрина снизило по сравнению с контролем кровопотерю свыше 400 *мл* в 8 раз (2,9 и 23,2). При этом роды, проходившие с массивной кровопотерей (более 800 *мл*), наблюдались в 9 раз реже у тех родильниц, которым применялся этот препарат (0,4 и 3,6%). Изменила свой характер и физиологическая кровопотеря. Кровопотеря от 30 до 200 *мл* была у 82,1% родильниц (в контрольной группе у 30,3%), от 201 до 300 *мл* — у 11,4% (в контроле у 23,5%) и от 301 до 400 *мл* — всего у 3,6%, т. е. у числа женщин в 6 раз меньше, чем в контроле (23%).

В связи с тем что метилэргометрин был рекомендован для профилактики кровотечений у рожениц с поздними токсикозами беременных и заболеваниями сердечно-сосудистой системы, особое значение приобретают сведения о влиянии этого препарата на показатели гемодинамики.

Метилэргометрин не оказал какого-либо влияния на изменение гемодинамических показателей у рожениц и родильниц с нормальным (163 наблюдения), повышенным (91 наблюдение) и пониженным (80 наблюдений) исходным уровнем артериального давления.

При анализе 210 поликардиограмм мы определяли продолжительность периода напряжения (фаза асинхронного и изометрического сокращения), периода изгнания, внутрисистолический показатель, индекс напряжения миокарда. Длительность фаз сердечного цикла, полученная в нашем исследовании, близка по значению к показателям С. Н. Томашевой и Н. Е. Орлянского, наблюдавших синдром гиподинамии у женщин в последние недели беременности по сравнению со здоровыми небеременными женщинами.

В исследуемой нами группе также были отмечены признаки нарастания синдрома гиподинамии. Однако тенденция к фазовому сдвигу в сторону гиподинамии была менее выражена и наблюдалась несколько позже (3-й час наблюдений), чем в контрольной (2-й час наблюдения) группе. Идентичность показателей в обеих группах отмечалась с 3-го по 4-й час наблюдения, что может быть обусловлено окончанием действия препарата.

При стабильности показателей гемодинамики наличие фазового сдвига в сторону гиподинамии следует рассматривать прежде всего как физиологическую реакцию сердечной мышцы на нагрузку, возникшую в процессе родов.

Можно отметить, что введенный метилэргометрин оказывает некоторое тонизирующее действие на миокард (позднее нарастание признаков гиподинамии и их меньшая выраженность в основной исследуемой группе).

В связи с тем что ряду исследователей (Л. В. Бокова и соавт.; О. Г. Петраш и соавт.; Santoni и соавт.) удалось определить возможность снижения свертывающих свойств крови при использовании препаратов, усиливающих сократительную способность матки (питуитрин, окситоцин, пахикарпин), мы провели изучение показателей свертывающей системы крови у 54 рожениц в первом периоде родов, в конце второго периода до введения препарата и через 15—60 мин. после его применения.

Введение метилэргометрина не оказало существенного влияния на изменение уровня фибриногена, но привело к некоторому снижению фибринолитической активности крови по сравнению с первым наблюдением до введения препарата. Показатели протромбинового индекса, времени рекальцификации плазмы, толерантности плазмы к гепарину после использования метилэргометрина существенно не изменились.

Результаты клинических наблюдений различных авторов (И. Штаркалев и соавт.; П. З. Гогилов) показали, что метилэргометрин повышает тонус маточной мускулатуры уже через 30—60 сек. после внутривенного

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TÉRATOLOGIE EXPÉRIMENTALE. — *L'effet tératogène du rétinol sur l'embryon de Poulet.* Note (*) de M. Armand Abramovici, présentée par M. Etienne Wolff.

Le rétinol, injecté chez les embryons de Poulet au 3e jour d'incubation, produit un effet létal limité. L'effet tératogène semble être influencé par la voie d'administration de la vitamine. A faibles doses la voie intravitelline est plus active (21,6 %) que la voie supra-blastodermique (11,4 %), tandis qu'à fortes doses l'effet tératogène est identique pour les deux voies (21,9 et 24,2 % respectivement). Les types d'anomalies observés sont très variés et certains d'entre eux montrent une spécificité de distribution selon la voie d'injection.

La plupart des travaux sur l'effet tératogène de l'hypervitaminose A concernent les Mammifères, en particulier les Rongeurs [(1) à (4)]. L'administration de vitamine A à fortes doses chez les embryons de Poulet âgés de 4 à 8 jours d'incubation, ne produit pas de malformations, sauf quelques altérations histologiques de l'œil (5). D'autre part l'effet de la vitamine A en excès, sur les Poules pondeuses, amène seulement un ralentissement de la ponte (6).

Le choix d'embryons âgés (5) et le manque de précisions sur la forme de la vitamine A utilisée, caractéristique des travaux antérieurs, augmentent les incertitudes dans la connaissance de l'effet tératogène réel de la vitamine.

Nous nous sommes donc intéressés à l'étude de l'effet tératogène de la vitamine A-alcool (rétinol) sur l'embryon de Poulet aux stades jeunes de développement en rapport avec la voie d'injection.

Matériel et méthodes. — Des œufs de Poulet de souche Leghorn blanche, sont ouverts et injectés au 3e jour d'incubation (stade 18 H et H).

Le rétinol (7) sous forme de cristaux est dissous d'abord dans l'éthanol pur, puis dilué avec du liquide de Tyrode sans Ca^{++} ni Mg^{++} jusqu'à la concentration finale désirée. Les doses sont exprimées en unités internationales (1 U. I. = 0,3 µg). Les solutions de rétinol sont administrées à l'aide d'un micro-injecteur d'Ancel (7) par deux voies d'injection différentes : la voie intravitelline (i. v.) et la voie supra-blastodermique (s. b.). La voie i. v. consiste en une injection directe dans le sac vitellin. La voie s. b. consiste à déposer la solution sur le mésoderme de l'aire vasculaire, à proximité de l'embryon, après avoir déchiré préalablement la membrane vitelline sus-jacente. Les embryons ainsi injectés sont incubés à 37,5 °C jusqu'au 13e jour d'incubation. On examine alors les embryons macroscopiquement pour déceler d'éventuelles anomalies.

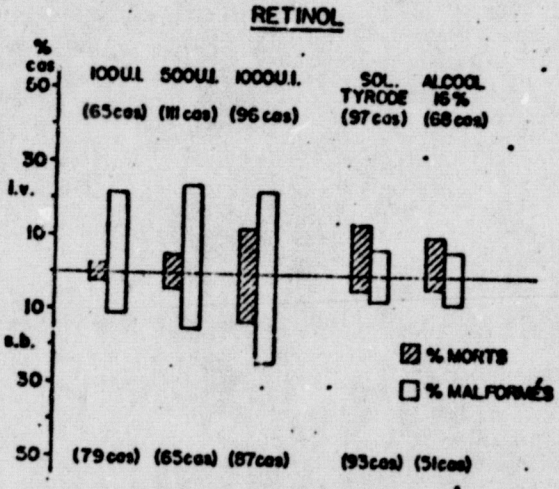
Résultats. — L'injection d'une dose de rétinol de 100 U. I./œuf provoque un effet létal très faible par les deux voies d'administration (3,5 % i.v. et 2,5 % s. b.). En augmentant dix fois la dose de vitamine, son effet létal ne s'accroît que de 4 à 6 fois (11,9 % i. v. et 13,9 % s. b.). Notons donc que l'effet létal du rétinol est identique, quelle que soit la voie d'administration (*fig.*).

Par contre, chez les témoins, l'effet létal est différent selon la voie d'injection

employée. Une solution de Tyrode sans Ca^{++} ni Mg^{++} provoque une mortalité de 13,4 % par la voie i. v. et de 4,3 % par la voie s. b.

L'injection d'une solution d'éthanol à 16 % (qui correspond à un volume d'éthanol contenu dans la solution de rétinol de 1 000 U. I./œuf) provoque un taux de mortalité de 10,3 % par voie i. v. et de 3,9 % par voie s. b.

L'effet tératogène du rétinol varie en rapport avec la voie d'administration (*fig.*). A faible dose, le rétinol est plus actif par la voie i. v. (21,6 %) que par la voie s. b. (11,4 %). Par contre, une forte dose de 1 000 U. I./œuf induit un effet tératogène identique pour les deux voies d'injection (21,9 et 24,2 % respectivement). Le taux de malformations chez les témoins est plus réduit (6,7 %), quelle que soit la voie d'injection utilisée.



L'effet létal et tératogène du rétinol selon la voie d'administration : voie intravitelline (i. v.), voie suprablastodermique (s. b.)

Nous avons remarqué que la distribution morphologique des malformations varie aussi selon la voie d'administration. Le rétinol injecté par la voie i. v. provoque des malformations cardio-vasculaires (8,8 %), cranio-faciales (2,2 %), des anouries (2,6 %) et des mésonéphros polycystiques (4,4 %); tandis que par voie s. b. la vitamine induit surtout des anouries (4,3 %), des malformations cardiovasculaires (2,7 %), du squelette et des membres (0,8 %). Notons que les malformations du squelette et des membres n'apparaissent pas chez les embryons traités par la voie i. v., et on ne trouve pas de mésonéphros polycystiques chez ceux qui sont traités par la voie s. b. Des malformations ayant un caractère généralisé (anasarque, sous-développement et cœlosomie) sont assez communes chez les embryons expérimentaux (3,5 % par voie i. v. et 8,6 % par voie s. b.) ainsi que chez les témoins (4,1 et 3,2 % respectivement).

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CONCLUSIONS. — L'effet létal du rétinol sur l'embryon de Poulet est limité pour les deux voies d'administration employées. Quant à l'effet tératogène, il semble être déterminé quantitativement et qualitativement par la voie d'injection utilisée. Par voie i. v le taux de malformations est assez élevé, et identique pour toutes les doses administrées, tandis que par voie s. b. l'effet s'accroît proportionnellement à la dose.

Les types de malformations obtenus semblent aussi influencés par la voie d'administration du rétinol. La présence de certaines anomalies dans un groupe expérimental et leur absence dans un autre peuvent suggérer un effet direct et localisé du rétinol, différent selon la voie d'injection utilisée.

Malgré la variabilité morphologique des malformations, l'effet tératogène de l'hypervitaminose A est quantitativement plus réduit chez les embryons de Poulet que chez ceux de Mammifères [(1) à (4)]. Une telle différence d'activité de la vitamine peut être expliquée, en partie, par une sensibilité différente des embryons de ces deux espèces (5).

Compte tenu de la différence de forme chimique de la vitamine A utilisée dans les travaux précédents, il nous semble difficile de comparer nos résultats avec ceux des autres auteurs. Une meilleure connaissance de l'activité embryotoxique des autres formes chimiques de vitamine A sur les embryons de différentes espèces s'impose donc.

(*) Séance du 10 mai 1971.

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HISTÓRICO

Até o século XVII, segundo Velázquez[11], era rara a ocorrência de raquitismo no mundo. Isso se deveu ao fato de que basta a irradiação solar diária de 10 cm² de pele, para que os

A dieta habitual de uma pessoa da classe média fornece-lhe cêrca de 4.000 UI de vitamina A e 400 UI de vitamina D por dia, que correspondem às suas necessidades. A ingestão de um suplemento vitamínico é tão desnecessária, nessas condições, como a complementação de qualquer outra necessidade fisiológica, nos limites da normalidade. Assim não fôra, teria sido impossível a vida humana, antes da descoberta das vitaminas.

Fraser[19] pensa coincidentemente ao afirmar que "*no supplemental vitamin D* (e isso se pode estender às demais) *is considered necessary for above that required ... diet and casual ex...*". É evidente que o ... excessivo às crianças ... ico-dietéticos adequa... que o mesmo autor ... de massa de adoles... , em algumas áreas, ... taxas de vitamina D ... UI por dia, sem con... ...sinoses A e D surgi... ...ência de tratamentos ... medidas governamen... ... Embora se saiba da ... administração dessas ... nados casos, o abuso ... a carecer, na sua es... ...icios que benefícios.

Vitamina A — É desconfiante: "*the typical lesions result from an acceleration of the constant process that takes place during maturation of bones*"[14]. Em clínica humana, Pearce[31] e outros[26,32] mostraram que ela inibe o crescimento ósseo e sua maturação, tornando o esqueleto mais frágil e sujeito a fraturas. A experimentação laboratorial confirmou que os achados clínicos se devem realmente à dieta vitamínica[3,8,29]. Outros efeitos que lhe têm sido imputados são lesões hepáticas[23,25], hidro e anencefalia[16,17], alterações nutritivas[27,28], lábio leporino[20] espinha bífida[9], catarata[5] e inúmeras outras anomalias

1. Vitamin deficiency et malformations foetales / Vitamin deficiency and fetal malformations. Arch. de pediat. 28:11/3/971 apud. in 12.3.71.

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Vitaminoterapia e malformações fetais[1]

Ério Brazil Pellanda*
Pôrto Alegre, RS

Tanto a hipo quanto a hipervitaminose materna podem ser causa de anomalias do concepto. Fatos sugestivos sôbre o assunto são conhecidos há 40 anos[14,25] e sua comprovação clínica e experimental é, hoje, indiscutível.

A indústria colabora na prevenção e tratamento das doenças carenciais, através de suas especialidades farmacêuticas mas, infelizmente, tem-se como certo que também é responsável — por motivos que escaparam ao contrôle científico de produção — pelo desencadeamento de afecções iatrogênicas caracterizadas por hipervitaminose.

Pouca atenção se tem dado ao problema, em nosso meio; assim, o objetivo do presente trabalho será o de divulgar dados recentes sôbre o assunto.

HISTÓRICO

Até o século XVII, segundo Velásquez[41], era rara a ocorrência de raquitismo no mundo. Isso se deveu ao fato de que basta a irradiação solar diária de 10 cm² de pele, para que os precursores da vitamina D do plasma sangüíneo nela se transformem em quantidade suficiente. A vida em maior contato com a natureza permitiu aos nossos ancestrais um metabolismo adequado dessa vitamina; a aglomeração em grandes centros citadinos determina cada vez menor exposição dos indivíduos ao sol. O raquitismo é, pois, doença da civilização e seu tratamento poder-se-ia limitar a medidas de ordem higiênica.

A hipovitaminose A é, sabidamente, decorrência de vício dietético, que pode ser corrigido com relativa facilidade.

HIPERVITAMINOSE

A dieta habitual de uma pessoa da classe média fornece-lhe cêrca de 4.000 UI de vitamina A e 400 UI de vitamina D por dia, que correspondem às suas necessidades. A ingestão de um suplemento vitamínico é tão desnecessária, nessas condições, como a complementação de qualquer outra necessidade fisiológica, nos limites da normalidade. Assim não fôra, teria sido impossível a vida humana, antes da descoberta das vitaminas.

Fraser[19] pensa coincidentemente ao afirmar que "*no supplemental vitamin D* (e isso se pode estender às demais) *is considered necessary for adults, over and above that acquired from the ordinary diet and casual exposure to sunlight*". É evidente que o mesmo critério é extensivo às crianças de hábitos higiênico-dietéticos adequados, uma vez que o mesmo autor calcula que grande massa de adolescentes nos EUA, em algumas áreas, certamente ingere taxas de vitamina D inferiores a 100 UI por dia, sem conseqüências.

As hipervitaminoses A e D surgiram como decorrência de tratamentos irracionais e de medidas governamentais precipitadas. Embora se saiba da necessidade de administração dessas substâncias em contados casos, o abuso da vitaminoterapia carrega, na sua esteira, mais malefícios que benefícios.

Vitamina A — É descalcificante: "*the typical lesions result from an acceleration of the constant process that takes place during maturation of bone*"[2]. Em clínica humana, Pease[31] e outros [2,37] mostraram que ela inibe o crescimento ósseo e sua maturação, tornando o esqueleto mais frágil e sujeito a fraturas. A experimentação laboratorial confirmou que [illegible] daquela vitamina[1,8,28]. Outros efeitos que lhe têm sido imputados são [illegible], hidro e anencefalia[3,17], alterações nutritivas[33,34], [illegible] e espinha bífida[9], catarata[5] e inúmeras outras anomalias

1. Vitaminoterapia e malformações fetais / [illegible] apresentado [illegible] em 13/3/71; aprov. em [illegible] 71.
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congênitas[1,9,22], além de um sem número de sinais e sintomas molestos[1,37,38,41]. Giroud e Martinet[42] obtiveram experimentalmente fetopatias com doses que, hoje, são fàcilmente superadas em clínica humana! Deve-se acrescentar que a cortisona e o metiltiuracil aumentam o efeito teratogênico da vitamina A[23].

Vitamina D — Com relação à intoxicação ocasionada pela vitamina D, a experiência é trágica e, por isso, comparada por Taussig[40] àquela ligada à ingestão de talidomida pela gestante: *"the decrease in the prevalence of idiopathic hypercalcemia was nearly as striking as the elimination of phocomielia in Germany after thalidomide was withdrown from the market"*. A chamada "hipercalcemia epidêmica" ocorreu na Inglaterra[36] e em parte na América do Norte [40], quando o govêrno dêsses países recomendou a adição de quantidade elevada de vitamina D ao leite distribuído à população; além disso, a indústria de alimentos pós à disposição dos usuários leite em pó e farinha de cereais "enriquecidos" dessa vitamina, em especial para lactentes e crianças. Sua ingestão indiscriminada, acrescida dos inefáveis "suplementos vitamínicos", gerou uma epidêmica forma de hipercalcemia, caracterizada por *facies* peculiar, estenose aórtica supravalvular, idiotia, calcinose, anomalias dentárias, hipercolesterolemia etc.[7,11,20,21,34,36,39]. Pode ocorrer arteriosclerose generalizada[36, 40] e a *"calcinosis may affect literally any tissue or organ of the body: the joints with their synovial membranes, alveoli of the lung, parathyroid glands, heart muscle, kidneys and the renal pelvis, skin, lymph nodes, pancreas, various arteries, lining wall of the stomach and even the cornea and conjuntiva"*. [4]. A experimentação animal reproduziu o síndrome em tôda a sua extensão[1,3,5,11,22]. Cabe destacar que a "hipercalcemia congênita" pode ocorrer em crianças cujas mães receberam doses que são apenas moderadamente superiores àquelas consideradas profiláticas[36] e que *"it has been reported in one instance that 400 units a day (vit. D) led to lesions that proved fatal"*[4].

ANOMALIAS CONGÊNITAS

As fetopatias congênitas em nossa clínica foram calculadas em aproximadamente 0,4%. Dos casos ocorridos e examinados, dentre aquêles em que não foi possível encontrar antecedentes familiares que os explicassem, ocorreu um que foi caracterizado como "artrogripose múltipla congênita" e a paciente inadvertidamente fizera o uso de 100.000 UI de vitamina A por dia, durante "alguns dias" (sic), no segundo mês de gestação. Há quinze anos vimos insistindo com nossas pacientes para que mantenham regime higiênico-dietético correto; nenhum "suplemento" vitamínico ou qualquer medicamento lhes foi prescrito, a não ser em caso de comprovada necessidade. A calcemia é solicitada com os exames iniciais: é um pobre recurso, mas sempre permite a avaliação indireta do metabolismo das vitaminas A e D, bem como a discussão do fato com a paciente.

São consideradas toleráveis e habituais taxas de 2 a 2,6% de malformações fetais na população em geral, para os países altamente industrializados[23]. Não possuímos, no Brasil, dados precisos sôbre o tema. Mas, a grande incidência de anomalias fetais que tem sido relatada naqueles países de elevado padrão de vida (EUA, Inglaterra, Suiça, Suécia, Alemanha, Canadá etc.) é de certa forma estarrecedora. Apgar[2] mostra que, segundo os autores, 30 a 60% de perdas fetais, no total de gestações, ocorre por anomalias incompatíveis com a sobrevivência. 24 a 50% dos abortos espontâneos até a vigésima semana de gestação aconteceram em função de malformações do embrião. Entre os fetos que sobrevivem ao parto, até 14% (Pennsylvania Lying-In Hospital) são ainda mal formados! As diferenças numéricas encontradas são tão díspares (24% e 50%, por exemplo) que fazem pensar na possibilidade, entre outras, de que os diversos grupos responsáveis pelo contrôle das pacientes possam estar a induzir-lhes afecções iatrogênicas.

Fraser[19], no estudo que fêz sôbre a "epidemia hipercalcêmica" inglêsa, encontrou números bem menos significativos. No entanto, é preciso lembrar que êle computou apenas os *sobreviventes* do evento, não levando em conta os abortos ocorridos nem tampouco os óbitos pós-natais que segundo Royer[34], apresentaram um índice de calcificação arterial de 12% em crianças falecidas por diversas afecções, na época, antes de atingirem a um ano de idade.

Appar[2], cautelosamente, não quis correlacionar diretamente dados tão impressionantes com a ingestão de vitaminas lipossolúveis. Outros o fizeram[7,36,40], pois quando se sabe que o número de absorções embrionárias é elevado nas experiências laboratoriais com essas substâncias e que os defeitos constatados na prole de animais submetidos à vitaminoterapia durante a gestação é quantitativa e qualitativamente comparável à que ocorre em clínica humana, o paralelo é ineludível.

INDÚSTRIA DE VITAMÍNICOS

Há vinte anos, as doses pró-dose ("doses por vez") de vitamina A e D que se encontravam nos produtos farmacêuticos à disposição do público eram de aproximadamente 400 e 40 UI, respectivamente. Tratavam-se de substâncias obtidas de fontes naturais, que são melhor metabolizadas pelo organismo que as sintéticas[41]. A síntese das vitaminas barateou seu custo de produção. Ràpidamente os laboratórios farmacêuticos passaram a oferecer "vantagens" aos médicos e ao público com a clássica fórmula de que "nosso preparado contém mais vitaminas por menor preço. O abuso foi o passo seguinte.

As aberrações que se constatam no preparo dêsses produtos farmacêuticos serão fàcilmente averiguadas pelo leitor que assim o desejar. Produtos há, recomendados entre outras indicações para "os períodos de gravidez", que fornecem 25.000 UI de vitamina A e 1.000 UI de vitamina D por dose: a recomendação é de duas cápsulas por dia! Outros, com teores semelhantes, possuem recomendações como "uma ou *mais* drágeas por dia", "três ou mais por dia"; as proposições assim vagas levam o médico pouco afeito ao problema e os pacientes às doses francamente tóxicas em curto espaço de tempo. É também o caso de nomes semelhantes como, digamos, "x com vitaminas" e "x simples": o primeiro forneceria, por si só, três vêzes os teores dessas vitaminas que a gestante deve obter de tôdas as fontes nutritivas de que dispõe. Pois já vimos colegas aconselharem o dôbro dessa dose, talvez traídos pela posologia proposta para o "x simples", que seria de seis comprimidos por dia. Há um produto que chega a propor para as grávidas a ingestão francamente tóxica de 10.000 UI de vitamina D por dia.

A desproporção entre as doses dessas vitaminas, de um para outro preparado, mostra também o total des-

conhecimento de [illegible] elaborados. Se [illegible] mantém hígido [illegible] um para dez (1:10 A, respectivamente oferece a natureza proporção existente, sob pena de o[illegible]bolização da substância ou, olhado o [illegible] aspecto, de não se efeitos tóxicos. Por riam dentro dos lim[illegible] nas alguns poucos [illegible] maioria, as propor[illegible] — passando por 1:1 — 1:5 — 1:2 — porção "dose por [illegible] uns contêm 2,5 de[illegible] para uma de vitam[illegible] outros para cada d[illegible] oferecem cinco de vi[illegible] clusão é de que n[illegible]te no mercado nen[illegible] gênero que possa s[illegible] prescrito para uso [illegible]

Está em tempo [illegible] macêutica encarar es[illegible] e com maior critério [illegible] ma de tamanha im[illegible] demais acrescentar a[illegible] Taussig[40]: *"My plea[illegible] doses of vitamin D [illegible] and there is any po[illegible] may do harm, do fol[illegible] if you cannot do goo[illegible] harm"*.

Quando se tornar [illegible] a insensatez que existe [illegible] doses elevadas de v[illegible] cialmente para gest[illegible] esta importante fonte [illegible] os laboratórios vai [illegible] demora. Urge, pois, [illegible] se atualize, colocando [illegible] classe médica fórmulas

FÓRMULA [illegible]

Qual deve ser o t[illegible] duto vitamínico para [illegible] pecial de vitaminas A [illegible] Se a paciente obtém [illegible] normal aquilo de que [illegible] há porque administrar [illegible] tos desnecessários: *"[illegible] for added vitamins for [illegible] son eating a well bal[illegible] is the goal of therapy"*. [illegible] um "suplemento" é [illegible] dável e a êsse critério [illegible] centar, a contrapeso, [illegible] A nossa ver, a d[illegible] um produto farmac[illegible]

conhecimento de causa com que são elaborados. Se nosso organismo se mantém higido com a proporção de um para dez (1:10) de vitaminas D e A, respectivamente, que é o que nos oferece a natureza, essa deveria ser a proporção existente nos medicamentos, sob pena de ocorrer maior metabolização da substância mais abundante ou, olhado o problema sob outro aspecto, de não se antagonizarem os efeitos tóxicos. Por êsse critério estariam dentro dos limites desejáveis apenas alguns poucos dêsses produtos. Na maioria, as proporções vão de 1:25 — passando por 1:15 — 1:7,5 — 1:6 — 1:5 — 1:2 — até 1:1,4. A proporção "dose por dose" mostra que uns contêm 2,5 doses de vitamina A para uma de vitamina D, enquanto outros para cada dose da vitamina A oferecem cinco de vitamina D... A conclusão é de que não existe atualmente no mercado nenhum produto dêsse gênero que possa ser tranqüilamente prescrito para uso profilático.

Está em tempo de a indústria farmacêutica encarar com mais seriedade e com maior critério científico problema de tamanha importância. Não é demais acrescentar aqui as palavras de Taussig[40]: *"My plea is that, if large doses of vitamin D are not necessary and there is any possibility that they may do harm, do follow the old adage: if you cannot do good, be sure not do harm"*.

Quando se tornar mais conhecida a insensatez que existe na prescrição de doses elevadas de vitamínicos, especialmente para gestantes e lactentes, esta importante fonte de divisas para os laboratórios vai estagnar. Isso não demora. Urge, pois, que a indústria se atualize, colocando ao dispor da classe médica fórmulas mais corretas.

FÓRMULA IDEAL

Qual deve ser o teor de um produto vitamínico para gestantes, em especial de vitaminas A e D, por dose? Se a paciente obtém da alimentação normal aquilo de que necessita, não há porque administrar-lhe complementos desnecessários: *"There is no need for added vitamins for a normal person eating a well balanced diet. This is the goal of therapy"*[4]. No entanto, um "suplemento" é às vêzes recomendável e a êsse critério se poderia acrescentar, a contragosto, o efeito placebo. A nosso ver, a dose pró-dose ideal de um produto farmacêutico dêsse tipo deve situar-se no limite de 1/10 da recomendada como dose total por dia, isto é, 400 UI de vitamina A e de 40 UI de vitamina D. Essas doses permitirão grande flexibilidade terapêutica e uma multiplicação adequada sem risco de intoxicação, na grande maioria dos casos. Apesar disso, escaparão a êsse limite de segurança os indivíduos hipersensíveis (hiper-reativos). A mesma proporção deve ser ideal para as outras vitaminas, o cálcio, o ferro, os oligominerais e quaisquer outros componentes da fórmula. É preciso ter-se em mente que "dose profilática" e "dose terapêutica" são conceitos diversos, que não devem convergir.

A prescrição de doses elevadas de vitaminas é irracional e o abuso de seu emprêgo em afecções não carenciais têm trazido sérios inconvenientes[15,37,38,40]. Pelo risco que pressupõem, os produtos farmacêuticos contendo doses superiores às fisiológicas deveriam se acompanhar de inscrição destacada, desaconselhando seu uso por parte de gestantes e lactentes.

COMENTÁRIOS

É sabido que há indivíduos portadores de afecções carenciais rebeldes à terapêutica. Entretanto, êsses contados casos não podem servir de orientação na fabricação de medicamentos, quando se pretende apenas suplementar um hipotético *deficit*, isto é, utilizar o medicamento de forma preventiva. Tanto mais que há também os casos de hiper-reatividade, que podem evoluir para o êxito letal — ou sofrer graves conseqüências orgânicas — mesmo com doses reduzidas de vitamínicos.

É possível que os danos causados pela vitaminoterapia intensiva não tenham sido maiores, porque se sabe que as vitaminas A e D se antagonizam em alguns de seus efeitos. Mas é evidentemente absurdo pretender-se, com êsse argumento, oferecer ao paciente dois venenos de uma só vez, ao invés de um. O organismo se defende da agressão: *"The body reacts to large doses of vitamins as it does to poisons by eliminating them in the urine, by inactivation or by chemical decomposition"*[4]. Quando não o consegue, desencadeiam-se a intoxicação e o dano tissular.

Inadvertidamente, os médicos — arrastados pela intensa propaganda laboratorial — impuseram o falso conceito, no público em geral, de que tôda grávida deve tomar suplemento vitamínico. Infelizmente, também julgaram estar se servindo apenas de um efeito placebo, ao prescreverem vitaminas para tôda e qualquer queixa da paciente. Parafraseando Bean[4]: *"I don't know what to do. Vitamins won't hurt. Let's try some vitamins"*. Êsses fatos tendem agora a se racionalizar e divulgar: ultrapassando a pesquisa pura, começam a ser discutidos e esclarecidos nos livros de texto[4,23,24] e mesmo nas revistas e jornais populares, através de suas seções de divulgação médica[2]. Antes que se generalize o conhecimento sôbre a extensão do dano que está sendo causado pela vitaminoterapia intensiva e indiscriminada, conviria que os laboratórios se antecipassem, com propaganda bem orientada, oferecendo produtos com fórmulas que estejam mais de acôrdo com o que aponta a pesquisa atual.

CONCLUSÕES

1) Nenhum produto farmacêutico à base de vitaminas, atualmente à disposição da classe médica, oferece segurança na prescrição. Contêm, todos, doses que são altamente deletérias, especialmente os destinados às mulheres grávidas, lactentes e crianças.

2) Urge que a indústria farmacêutica atenda ao chamamento da pesquisa, atualizando as fórmulas de seus produtos manufaturados, dentro dos padrões apontados.

3) Até que isso ocorra, cumpre aos médicos e às entidades de classe favorecer ampla campanha no sentido de esclarecer a população em geral quanto aos malefícios da ingestão indiscriminada de vitaminas lipossolúveis.

RESUMO

O autor analisa produtos farmacêuticos atualmente em uso por parte das gestantes, cujo conteúdo em vitaminas A e D julga excessivo. Mostra a possibilidade de se correlacionar êsse fato com o desenvolvimento de anomalias fetais, como se tem observado tanto em clínica humana, quanto experimentalmente. Partindo do princípio de que a gestante não necessita obrigatòriamente de " suplementos vitamínicos" além do

2. Knoplich, J. (rev. Manequim): "Foi constatado que em cidades inteiras surgentes o índice de cáries, devido ao excesso de flúor na água potável".

que obtém de uma alimentação adequada, propõe que os laboratórios farmacêuticos ponham à disposição da classe médica produtos que contenham 400 e 40 UI por dose de vitaminas A e D, respectivamente. Essas doses permitirão grande flexibilidade terapêutica e multiplicação adequada, sem risco de provocarem intoxicação ou fetopatias.

RÉSUMÉ

Vitaminothérapie et malformations foetales

L'auteur analyse des produits pharmaceutiques en usage actuellement par des femmes enceintes, dont le contenu de vitamines A et D il juge excessif.

Il montre la possibilité de se tenir une corrélation entre ce fait et le développement des anomalies foetales, ce qu'on a observé soit chez la clinique humaine, soit dans les expérimentations.

A partir du principe que la femme enceinte n'a pas obligatoirement besoin des "suppléments vitaminiques" outre ceux qu'elle obtient d'une alimentation conforme, il propose aux laboratoires pharmaceutiques de disposer à la classe médicale des produits qui contiennent 400 et 40 UI de vitamines A et D, respectivement par dose. Ces doses permettront une grande flexibilité thérapeutique et multiplication adéquate, sans risque de provoquer intoxication ou foetuspathies.

SUMMARY

Vitamin therapy and fetal malformations

The author discusses the pharmaceutical products presently used by pregnant women, whose vitamin A and D content he considers excessive. He demonstrates the possibility of correlating this fact with the development of fetal anomalies for it has been observed in human beings as well as experimentally. Based on the fact that a pregnant woman does not necessarily need a 'vitamin supplement' in addition to what she normally receives from an adequate diet, he proposes that the pharmaceutical laboratories place on the market products containing 400 and 40 UI per dose of vitamin A and D respectively. These doses will permit a greater therapeutic flexibility and adequate multiplication without the risk of inducing intoxications or fetal anomalies.

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Hydergin. Aus der Abbildung ist eindeutig zu ersehen, daß Hydergin sowohl die Wirkung des blutdrucksteigernden Noradrenalins wie auch den Effekt des blutdrucksenkenden Isoproterenols verstärkt, während es den Effekt der Carotis-Sinus-Entlastung fast auslöscht. Adrenalin verhält sich in dieser Versuchsanordnung genauso wie Noradrenalin. Die Abbildung zeigt eindeutig, daß nach Hydergin nur die vasomotorische Regulation beeinträchtigt bzw. gestört ist und daß infolge dieser Störung sowohl pressorische wie auch depressorische Effekte verstärkt in Erscheinung treten. Die Abbildung zeigt weiter, daß auch das im Hydergin vorliegende Gemisch der 3 hydrierten Alkaloide der Ergotoxingruppe noch eine eindeutige blutdrucksteigernde Wirkungskomponente aufweist.

Abbildung 2 zeigt die Wirkung von Ergotamin („Gynergen") an einem Versuch nach Entzüglungshochdruck (1. Abschnitt) und Dekapitierung (2. Versuchsabschnitt). In dem 3. Versuchsabschnitt wurde vor der Applikation von Ergotamin eine fortlaufende Dauerinfusion von 0,5 µg/kg/Min. Noradrenalin eingeleitet. Ergotamin wirkt hier in einer Dosierung von 25 µg/kg intravenös beim Entzüglungshochdruck blutdrucksenkend, während es bei dem durch eine Dauerinfusion von Noradrenalin herbeigeführten Hochdruck keine Wirkung aufweist. Dieser Versuch dürfte eindeutig zeigen, daß Ergotamin in der hier gewählten Dosierung überhaupt keine adrenolytische Wirkung ausübt, aber einen sehr starken Effekt auf den durch die Entzüglung hervorgerufenen Hochdruck aufweist.

Tabelle 1: Mittlere wirksame Dosierungen von Mutterkornalkaloiden gegenüber der Carotis-Sinus-Entlastung in i.v. (95%-Sicherheitsgrenzen. Dosierungen in µg/kg i. v.

Ergocristin	6,5	(4,75 — 8,05)
Dihydroergocristin	11,2	(8,55 — 14,7)
Ergotamin	22	(18,5 — 26,2)
Dihydroergotamin	41	(28,6 — 57,5)
Hydergin®	33,4	(18 — 30,4)

Die quantitative Auswertung zeigte die in der Tabelle niedergelegten Resultate. Sie bezieht sich selbstverständlich nur auf den Antagonismus gegenüber der Carotis-Sinus-Entlastung. Die nicht eingetretene bzw. bei den gewählten Dosierungen nicht vorhandene adrenolytische Wirkung konnte einer quantitativen Auswertung nicht unterworfen werden. Die nicht ausgewerteten Alkaloide der Ergotoxingruppe Ergocryptin und Ergocornin erschienen etwas schwächer als Ergocristin; wir möchten jedoch vermeiden, aus diesem Eindruck irgendwelche Schlüsse zu ziehen. Sicher ist jedenfalls, daß die Wirkung der hydrierten Alkaloide ganz allgemein schwächer ist als die Wirkung der genuinen Alkaloide. Die stärkste Wirkung zeigt offensichtlich das Ergocristin, demgegenüber zeigt Dihydroergotamin die relativ schwächste Wirkung gegenüber der Carotis-Sinus-Entlastung. Der Vorteil der hydrierten Alkaloide (geringere gefäßverengende Wirkung) wird durch eine schwächere Wirkung auf die zentrale Kreislaufregulation ausgeglichen. Es ist demnach nicht unbedingt sicher, daß die Einführung der hydrierten Alkaloide unbedingt und in jedem Falle einen therapeutischen Fortschritt bedeutet.

Diskussion

Eine weitergehende Diskussion dürfte sich erübrigen. Der Wert der vorliegenden Arbeit liegt u. E. darin, daß aufgrund ihrer pharmakologischen Art te Mutterkornalkaloide durchgeführt worden s

Zus

Es wird über eine geringe Dosierungen kornalkaloide gegen lastung. Noradrenalin eingesetzt wurden. D kornalkaloide in Dos beim Hund in Morg tensive Dämpfung de eine eindeutige adre festgestellt werden. wirksamen Dosierun genüber der Carotis-

Krause, D., D. Moursi Ali: C adrenolytic effect o loids

In a series of expe hydrated ergot alkal noradrenalin, adrena that ergot alkaloids nously cause in dog intensive suppressio was no clear adrenol

Für die fleißige danken wir den H K. Müller, J. Ja pflegern K. Brau

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Beitrag zur Frage der Embryotoxizität von Vitamin A

Von M. Seidler — Mit 2 Abbildungen und 1 Übersicht

Aus dem Institut für Pharmakologie, Toxikologie und Pharmazie der Tierärztlichen Hochschule, Hannover - Direktor: Prof. Dr. K. Kaemmerer

Allgemeines

In der Literatur finden sich widersprüchliche Angaben über die orale Dosierung von Vitamin A um teratogene Effekte hervorzurufen. So gab Coblan (1953) in seinen Versuchen trächtigen Ratten über mehrere Tage hinweg jeweils eine Dosis von 35 000 I. U. einer wäßrigen Vitamin A-Lösung. Er erhielt verringerte Würfe mit mißgebildeten Feten. Giroud und Martinet (1956) verabreichten Wistarratten von 200 g vom 4. bis 12. Tag der Gestation per os öliges Vitamin A in einer täglichen Dosis von 35 000 I. U. Alle Feten wurden abgestorben und resorbiert. In einem weiteren Versuch wurden täglich 20 000 I. U. über 12 Tage gegeben. Neben einem hohen Prozentsatz von Resorptionsstellen fanden sie 59% der Feten mißgebildet. Die Applikation von je 60 000 I. U. an drei aufeinanderfolgenden Tagen ergaben u. a. Anencephalien, Gaumenspalten und Anophthalmien (Giroud — Martinet, 1956). Filippi (1956) verabreichte Vitamin A-Palmitat in öliger Lösung am 11., 12., 13. bzw. 14., 15. und 16. Tag der

Übersicht: Dosierung, Zeitpunkt der Applikation und Befunde nach Vitamin-A-Gabe

	Versuchstiere	Dosis in I. U.	Tag p. c. der Applikation	Beobachtete Veränderungen
Ölige Vitamin-A-Palmitat	6	3 × 60 000	11., 12., 13. / 12., 13., 14. / 13., 14., 15.	—
	1	3 × 80 000	9., 10., 11.	—
	1	1 × 100 000	14.	—
	1	1 × 120 000	10.	—
	3	2 × 120 000	10., 11.	1 Wurf: Exophthalmien mißgebildete Ohren
	3	2 × 120 000	12., 13.	—
Ölige Vitamin-A-Palmitat	2	2 × 600 000	12., 13.	1 Wurf: Gaumenspalten, Knochen der Vorder- und Hinterextr. verkürzt
	1	2 × 600 000	14., 15.	—
	2	2 × 750 000	12., 13.	Nur Resorption

Im 22. Tag p. c. erfolgte die Gewinnung [illegible] durch Sectio caesarea. Adspektion der Feten auf äußere Mißbildungen und auf Gaumenspalten unter der Lupenmikroskop schloß sich an. Weiterhin wurde der gesamte Wurf nach Kaemmerer und Seidler (1969) gefärbt und mit Hilfe eines „Kindermann-Betrachtungsgerätes" ausgewertet.

Befund

In der Dosierung von 60 000 I. U. Vitamin A-Palmitat pro Tier — jeweils an drei aufeinanderfolgenden Tagen — konnten keine mißgebildeten Feten beobachtet werden. Auch eine Erhöhung der täglichen Dosis auf 80 000 I. U. ließ keine fetotoxische Wirkung erkennen. Erst die orale Applikation von je 120 000 I. U. Vitamin A-Palmitat am 10. und 11. Tag p. c. ergab einen

Abb. 2: Vitamin A-Palmitat per os. 10. u. 11. Tag p. c. je 120 000 I. U.

E143

s der Abbildung ist eindeutig zu ersehen, ...t sowohl die Wirkung des blutdrucksteigernden ...ins wie auch den Effekt des blutdrucksenkenden Isoproterenols verstärkt, während es ...al der Carotis-Sinus-Entlastung fast auslöscht. ...ch verhält sich in dieser Versuchsanordnung ...t wie Noradrenalin. Die Abbildung zeigt eindeutig ...dem Hydergin nur die vasomotorische Regulation ...sentlich abgeschwächt bzw. gestört ist und daß infolge dieser Störung schon pressorische wie auch depressorische Effekte verstärkt in Erscheinung treten. Die Abbildung ist weiter zu entnehmen, daß auch das im Hydergin vorliegende Gemisch der 3 hydrierten Alkaloide der Ergotoxingruppe eine eindeutige blutdrucksteigernde Komponente aufweist.

...bildung 2 zeigt die Wirkung von Ergotamin ...ch i. v. an einem Versuch nach Entzug (Abschnitt 1). Abschnitt und Exzerpierung (2. Versuchsabschnitt). In dem 2. Versuchsabschnitt wurde vor der ...ahme von Ergotamin eine fortlaufende Dauerinfusion von 0,2 µg/kg/Min. Noradrenalin eingeleitet. Wie aus der Abbildung zu ersehen ist, wird Ergotamin in einer Dosierung von 25 µg/kg ...ine durch Entzugshochdruck blutdrucksenkende Wirkung ...t. Es kann durch eine Dauerinfusion von Noradrenalin ...rbeigeführten Hochdruck keine Blutdrucksenkung ...ufweist. Dieser Versuch dürfte eindeutig zeigen, daß Ergotamin in der hier gewählten Dosierung keine adrenolytische Wirkung ausübt, aber ...rmutlich einen Effekt auf den durch die Entziehung ...rsachten Hochdruck aufweist.

...elle 1: Mittlere wirksame Dosierungen von Mutterkornalkaloiden gegenüber der Carotis-Sinus-Entlastung ...ie 95%igen Sicherheitsgrenzen Dosierungen in µg/kg i. v.

...rstein	6.3	(4.75 — 9.05)
...ydrogenergotamin	11.2	(8.55 — 14.7)
...min	22	(16.5 — 29.2)
...ydrogenergotamin	41	(28.8 — 57.5)
...gin	23.4	(18 — 30.6)

...e quantitative Auswertung zeigte die in der ...ehenden Tabelle 1 zusammengefaßten Resultate. Sie bezieht sich somit nur auf den Antagonismus gegenüber der Carotis-Sinus-Entlastung. Die nicht eingetretene bzw. in den gewählten Dosierungen nicht vorhandene adrenolytische Wirkung konnte einer quantitativen Auswertung nicht unterworfen werden. Die nicht ausgewerteten Alkaloide der Ergotoxingruppe Ergocryptin und Ergocornin erschienen etwas schwächer als Ergotamin, wir möchten jedoch vermeiden, aus diesem Eindruck irgendwelche Schlüsse zu ziehen. Sicher ist jedenfalls, daß die Wirkung der hydrierten Alkaloide ganz allgemein schwächer ist als die Wirkung der genuinen Alkaloide. Die stärkste Wirkung zeigt offensichtlich das Ergocristin, demgegenüber zeigt Dihydroergotamin die relativ schwächste Wirkung gegenüber der Carotis-Sinus-Entlastung. Der Vorteil der hydrierten Alkaloide (geringere gefäßverengende Wirkung) wird durch eine schwächere Wirkung auf die zentrale Kreislaufregulation ausgeglichen. Es ist demnach nicht unbedingt sicher, daß die Einführung der hydrierten Alkaloide unbedingt und in jedem Falle einen therapeutischen Fortschritt bedeutet.

Diskussion

Eine weitergehende Diskussion dürfte sich ...brigen. Der Wert der vorliegenden Arbeit liegt u. E. darin, daß aufgrund ihrer Resultate die meisten früheren pharmakologischen Arbeiten über genuine und hydrierte Mutterkornalkaloide mit zu hohen Dosierungen durchgeführt worden sind.

Zusammenfassung

Es wird über eine Versuchsreihe berichtet, bei der geringe Dosierungen genuiner und hydrierter Mutterkornalkaloide gegenüber der Carotis-Sinus-Entlastung, Noradrenalin, Adrenalin und Isoprotenol eingesetzt wurden. Die Arbeit zeigt, daß die Mutterkornalkaloide in Dosierungen unter 100 µg/kg i. v. beim Hund in Morphin-Chloralose-Narkose eine intensive Dämpfung der Kreislaufregulation hervorrufen; eine eindeutige adrenolytische Wirkung kann nicht festgestellt werden. Es wird eine Tabelle der mittleren wirksamen Dosierungen der Mutterkornalkaloide gegenüber der Carotis-Sinus-Entlastung angeführt.

Krause, D., D. Schmidtke-Ruhnau and M. Moursi Ali: Central sympathicus suppression and adrenolytic effect of genuine and hydrated ergot alkaloids

Summary

In a series of experiments small dosages of genuine and hydrated ergot alkaloids were used in comparison with noradrenalin, adrenalin and isoproterenol. It was shown that ergot alkaloids in dosages under 100 µg/kg intravenously cause in dogs with morphin-choralose narcosis an intensive suppression of the circulatory regulation. There was no clear adrenolytic effect.

Für die fleißige und schwierige technische Mithilfe danken wir den med.-techn. Assistentinnen S. Döbke, K. Möller, J. Janssen (geb. Büker) sowie den Tierpflegern K. Brandes und K. Gardle.

Anschrift des Verfassers: Prof. Dr. D. Krause I, 1 Berlin 33, Koserstraße 20.

...ag zur Frage der Embryotoxizität von Vitamin A

Seidler — Mit 2 Abbildungen und 1 Übersicht

...m Institut für Pharmakologie, Toxikologie und Pharmazie der Tierärztlichen Hochschule Hannover - ...or: Prof. Dr. K. Kaemmerer

Allgemeines

...er Literatur finden sich widersprüchliche Angaben ...r die orale Dosierung von Vitamin A um teratogene Effekte hervorzurufen. So gab Cohlan (1953) ...m Verfahren trächtigen Ratten über mehrere Tage ...ral per os eine Dosis von 35 000 I. U. einer ...en Vitamin A-Lösung. Er erhielt verringerte ...ahlen missgebildete Feten. Giroud und Martinet (1955) verabreichten Wistarratten von 200 g vom 9. Tag der Gestation per os öliges Vitamin A in einer täglichen Dosis von 35 000 I. U. Alle Feten waren abgestorben und resorbiert. In einem weiteren Versuch wurden täglich 20 000 I. U. über 12 Tage gegeben. Neben einem hohen Prozentsatz von Resorptionsstellen fanden sie 55% der Feten mißgebildet. Die Applikation von je 60 000 I. U. an drei aufeinanderfolgenden Tagen ergaben u. a. Anencephalien, Gaumenspalten und Anophthalmien (Giroud — Martinet, 1956). Filippi (1956) verabreichte Vitamin A-Palmitat in öliger Lösung am 11., 12., 13. bzw. 14., 15. und 16. Tag der

Übersicht: Dosierung, Zeitpunkt der Applikation und Befunde nach Vitamin-A-Gabe

	Versuchstiere	Dosis in I. U.	Tag p. c. der Applikation	Beobachtete Veränderungen
öliges Vitamin-A-Palmitat	4	3 × 60 000	11., 12., 13. / 12., 13., 14. / 13., 14., 15.,	—
	1	3 × 60 000	9., 10., 11.,	—
	1	1 × 100 000	14.,	—
	1	1 × 120 000	10.,	—
	3	2 × 120 000	10., 11.,	1 Wurf: Exophthalmien, mißgebildete Ohren
	3	2 × 120 000	12., 13.,	—
öliges Vitamin-A-Acetat	3	2 × 600 000	12., 13.,	1 Wurf: Gaumenspalten, Knochen der Vorder- und Hinterextr. verkürzt
	1	2 × 600 000	14., 15.,	—
	2	2 × 750 000	12., 13.,	Nur Resorption

Ges...tion in einer Dosierung von 60 000 I. U. In der ers... Gruppe fand er zu 88% Gaumenspalten, in der zw...en Gruppe zu 100%. Auch Wilson (1963) weist auf ...e teratogene Wirkung des Vitamin A hin. Nach die... Angaben liegen die Gesamtdosen, die Giroud — Martinet bzw. Filippi applizierten, zwi...hen 180 000 und 385 000 I. U. öligem Vitamin A, um embryotoxische Wirkungen hervorzurufen. Aus diesem Grunde schien es angebracht, diese Werte noch einmal zu überprüfen.

Methodik

...r diese Versuche standen männliche und weibliche Wistarratten (Brunger Wistar II) im Verhältnis 1:4 zur Verfügung. Die Haltung der Tiere erfolgte in abgedunkelten Isolierstallungen mit einer eingestellten Raumtemperatur von 22 ± 2° C bei einem Lichtprogramm von 12 Stunden. Als Behältnisse fanden Makrolonkäfige mit einer Einstreu aus Hobelspänen Verwendung. Wasser stand in Tränkflaschen ad libitum zur Verfügung. Gefüttert wurde gemahlenes Schweinealleinfutter des Raiffeisen-Kraftfutterwerkes in Aurich.

Die Ratten wurden nach entsprechender Eingewöhnungszeit (Gewicht: ♂♂ ab 250 g, ♀♀ ab 180 g) jeweils über Nacht gepaart. Konnte bei der morgendlichen Scheidenadspektion ein Vaginalpfropf oder -belag festgestellt werden, wurde das entsprechende Tier gekennzeichnet und gewogen. Dieser Tag wurde als 1. Tag p. c. (post coitum) bezeichnet.

Vitamin A-Palmitat stand als „A-Vicotrat"-Oleosum (Heyl-Berlin) zur Verfügung. Öliges Vitamin A-Acetat wurde von der Firma Merck-Darmstadt bezogen. Die Behandlung wurde in verschiedenen Dosierungen zwischen dem 9. und 15. Tag p. c. vorgenommen (s. Übersicht). Die einzelnen Dosen wurden ...mit Hilfe einer Stahlsonde appliziert.

Am 22. Tag p. c. erfolgte die Gewinnung der Feten durch Sectio caesarea. Adspektion der Feten auf äußere Mißbildungen und auf Gaumenspalten unter dem Lupenmikroskop schloß sich an. Weiterhin wurde der gesamte Wurf nach Kaemmerer und Seidler (1960) geröntgt und mit Hilfe eines „Kindermann-Betrachtungsgerätes" ausgewertet.

Befund

In der Dosierung von 60 000 I. U. Vitamin A-Palmitat pro Tier — jeweils an drei aufeinanderfolgenden Tagen — konnten keine mißgebildeten Feten beobachtet werden. Auch eine Erhöhung der täglichen Dosis auf 80 000 I. U. ließ keine fetotoxische Wirkung erkennen. Erst die orale Applikation von je 120 000 I. U. Vitamin A-Palmitat am 10. und 11. Tag p. c. ergab einen

Abb. 1: Fetus unbehandelt

Wurf, dessen Feten Exophthalmien sowie Ohrendeformationen aufwiesen (s. Abb.) Gaumenspalten und Knochenverkürzungen der Vorder- und Hinterextremitäten wurden bei sämtlichen Feten eines Wurfes — nach Behandlung von je 600 000 I. U. Vitamin A-Acetat am 12. und 13. Tag p. c. — gefunden. Eine Erhöhung der Dosis auf je 750 000 I. U. führte zur Resorption aller Feten.

Diskussion

Im Gegensatz zu den Ergebnissen von Giroud — Martinet und Filippi konnten nach dreimaliger Applikation von 60 000 I. U. bzw. 80 000 I. U. Vitamin A-Palmitat mißgebildete Rattenfeten nicht beobachtet

Abb. 2: Vitamin A-Palmitat per os. 10. u. 11. Tag p. c. je 120 000 I. U.

...ten die zweimalige Gabe von 120 000 ... einem Wurf Schädigungen hervorgerufen ... nicht den Schweregrad erreichten, der ... beschrieben wurde. Erheblich höhere ... scheinen notwendig zu sein, um Mißbildungen wie z. B. Gaumenspalten zu erhalten. Hierbei ... auch einige Faktoren, wie Rattenstamm, Zeitpunkt der Applikation und vor allem das verwendete Präparat nicht außer acht gelassen werden.*)

Zusammenfassung

Im Gegensatz zu den Angaben in der Literatur konnte nach einer dreimaligen oralen Applikation von ... I. U. Vitamin A-Palmitat bei dem verwendeten Rattenstamm keine teratogenen Schädigungen beobachtet werden. Erst die zweimalige Behandlung trächtiger Ratten mit je 120 000 I. U. Vitamin A-Palmitat bzw. 600 000 I. U. Vitamin A-Acetat ergab mißgebildete Rattenfeten.

Seidler, M.: Contribution to the problem of embryotoxicity of vitamin A

Summary

In contrast to the literature teratogenic effects were not observed after threefold administration of 60 000 I. U. vitamin A palmitate in rats. After the twice repeated treatment of pregnant rats with 120 000 I. U. vitamin A-palmitate or 600 000 I. U. vitamin A-acetate malformed rat fetuses occured.

Schrifttum

Cohlen (1953) zit. aus Kalter, H. (1966): Teratology of the Central Nervous System; The University of Chicago Press. — Filippi, B. (1956): Minerva Chirurgica XI, 1314—... — Giroud, A. und M. Martinet (1955): Int. Zeitschr. Vit.-Forschung 26, 10—18 — Kaemmerer, K. und M. Seidler (1970): Dtsch. tierärztl. Wschr. 77, 313—317. — Neu, G. A. (1959): Fd. Cosmet. Toxicol. 7, 205—216. — Wilson, J. G. (1965): Teratology; The University of Chicago Press.

Anschrift des Verfassers: Dr. M.-J. Seidler, 3 Hannover, Bischofsholer Damm 15.

*) Anmerkung: Diese Auffassung wird von Nolen (1969) bestätigt, der Stammesunterschiede nicht nur hinsichtlich Gesamthäufigkeit der Mißbildungen, sondern auch bei Verteilung der Mißbildungen in der Nachkommenschaft nach oraler Applikation von wäßrigem Vitamin A beobachtete.

Thermovision als Meßsystem in der Pharmakologie

Von K. Kaemmerer und S. Buntenkötter — Mit 4 Abbildungen

Aus dem Institut für Pharmakologie, Toxikologie und Pharmazie der Tierärztlichen Hochschule Hannover (Direktor: Prof. Dr. K. Kaemmerer)

Vorbemerkung

Seit geraumer Zeit bemühen wir uns im hiesigen Institut um Meßmethoden zur Erfassung vegetativer Reaktionen und Reaktionslagen. Hierbei erscheint uns für unsere Fragestellung die Aussage einer isolierten Reaktion oder einer auf ein einzelnes Organ beschränkten Reaktionsantwortung weniger bedeutsam als die Aussage, die evtl. am Gesamtkörper des Tieres meßtechnisch registriert werden kann. Wenn man von den bekannten, z. B. der Telemetrie oder anderen registrierenden Verfahren wie dem der Erfassung galvanischer Hautreflexe, des Elektrodermatogrammes und der Plethysmographie (Regelsberger, 1952; Frankenau, 1962; Gutmann, 1967; Janisch, 1965; Polzer, 1967) absieht, bietet sich die Thermovision als ergänzendes System an. Nachdem es uns jedoch im Verlauf mehrerer Jahre nicht gelungen ist, die notwendigen finanziellen Quellen hierfür zu erschließen, halten wir es zwar für ungewöhnlich, jedoch für angebracht, an dieser Stelle unsere Gedanken und Pläne sowie unsere ersten Erfahrungen mit diesem System in der Hoffnung bekanntzugeben, daß sie anderenorts als Anregung dienen und der Verwirklichung zugeführt werden können, da sie hier unter den obwaltenden Verhältnissen kaum mehr in Angriff genommen werden können.

Es bietet die Thermovision neben ihrem Wert für die klinische Diagnostik neue großartige Möglichkeiten gerade für den weiten Bereich der pharmakologischen Forschung und in Verbindung mit der Therapie auch für die Kontrolle von Arzneimittelwirkungen.

Das Meßsystem

Die Thermovision*) umfaßt eine Teiltechnik der Thermographie. Die Thermovision-Einheiten bestehen aus der Kameraeinheit und der Bildwiedergabeeinheit.

Eine spezielle Infrarotkamera dient zum schnellen Abtasten des Objektes. Die Infrarotstrahlung wird auf einem speziellen Detektor fokussiert, der seinerseits die Strahlung in elektrische Impulse umwandelt. Diese werden in der Bildwiedergabeeinheit verarbeitet. Letztere besteht aus einem besonders gearbeiteten Oszilloskop zur Wiedergabe des Wärmebildes auf dem Bildschirm. Es gelingt, Wärmetönungen der verschiedensten Art mit Differenzen bis zu 0,2 °C direkt zu messen, selbst wenn sie auf Oberflächen verteilt sind. Mit Hilfe von einzulegenden Isothermen ist es möglich, die verschiedenen Bezirke einander quantitativ zuzuordnen und zu bewerten. Das Fernsehsystem mit infrarotempfindlichen Wärmedetektoren auf Indium-Antimonid-Basis erlaubt die schnelle, ohne Zeitfaktor arbeitende Wahrnehmung verschiedenster Wärmebilder, die ihrerseits durch zum Aufnahmegerät gehörende Kameraeinrichtungen serienmäßig dokumentiert, d. h. fotografiert oder gefilmt werden können.

Anwendungsbereiche

Offensichtlich bleibt die Thermovision in ihrer Anwendung nicht auf industrielle Zwecke beschränkt. In der klinischen Medizin eröffnen sich bereits interessante Aspekte, die von der Tumordiagnostik über die Erfassung von entzündlichen Prozessen, von Brandwunden und Frostschaden bis zur Prüfung der Lebensfähigkeit von Hauttransplantaten und vielen anderem mehr reichen (siehe auch Notter u. M., 1968; Wehner, 1965).

Im Rahmen der Veterinärmedizin wurden Entzündungsprozesse an Sehnen und Sehnenscheiden bei Rennpferden klinisch untersucht und der Therapieverlauf kontrolliert. Diese Untersuchungen sind auch nicht publiziert, sie wurden an der Universität Stockholm durchgeführt (mündliche Mitteilung des Herstellers). Inzwischen erschien im deutschsprachigen Bereich auch eine Arbeit von Leidl (1970) über Untersuchungen am Genitalapparat.

Wir hatten drastische Pläne, die durch Erfassen somatischer wie tonischer Vorgänge in mancher Hinsicht für Theorie und Praxis Erfolg versprachen. Der Vorteil hätte unbestritten darin gelegen, Meßwerte von Tieren

*) Anmerkung: AGA-Thermovision, Hanseatische AGA-Gas GmbH, Hamburg 1, Große Allee 10

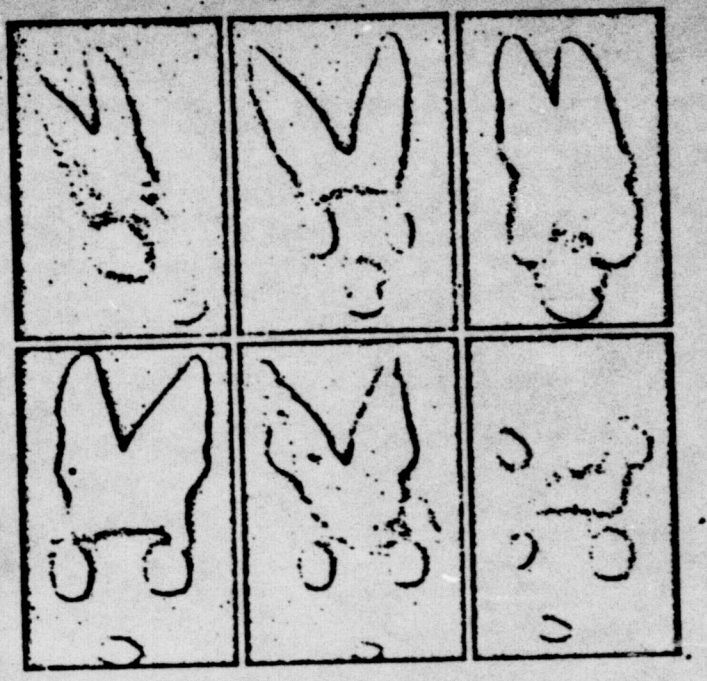

Abb. 1: Oben: *Beispiele für das Verhalten der Kaninchenohren nach Pyrifer 0,1 ml/kg i. v. vor, 5 Min. und 9 Min. post inj.* — Unten: *Beispiele für das Verhalten der Kaninchenohren nach Phenäthanolaminsulfat 2 mg/kg i. v. vor, ½ und 1 Min. post inj.; „Streifen" = eingelegte Isothermen*

zu erhalten, die keinem Zwang unterworfen worden wären, ein Fehler zahlloser Versuche, deren Palette von der Stress-auslösenden Fesselung über die Zwangshaltung bis zur Narkose reicht.

Wenn man unterstellt, daß zahlreiche Funktionen des Organismus vegetativ übersteuert sind, so wird sich dies als Ausdruck der vegetativen Ausgangslage auch am Stoffwechsel kundtun und mit ihm die Körpertemperatur variieren. Hier kann wiederum das Gesamtwärmemuster genauso bedeutsam sein wie die örtliche Kapillarfunktion, die sozusagen als „Meßstelle" figuriert.

Bisher mangelte es im Rahmen der Veterinärmedizin an diagnostischen Möglichkeiten, vegetative Reaktionslagen zu erfassen. Die vegetativen Dystonien wurden übersehen, so als ob es sie nicht gäbe, obwohl vielleicht gerade das Schwein die Funktion eines Managers im Tierstall übernimmt und extreme Umweltbelastungen mit dem „Herztod" quittiert. Die Messung vegetativer Reaktionen in Verbindung mit den Aussagen isolierter kontrollierter Organe (EKG, EEG, Respiration) weist mannigfaltige neue methodische Wege auch für Antworten auf umweltbedingte Verhaltensreaktionen. Es erscheint nicht als ausgeschlossen, reziprok innervierte Vorgänge zu analysieren, die sympathikotone Temperatursteigerung als Ausdruck bestimmter Stoffwechsellagen in spezieller Weise zu registrieren oder Angriffspunkte krisenhafter Kreislaufbelastungen am peripheren Reaktionsverhalten der Hautkapillaren aufzudecken.

Vielleicht gelingt es in diesem Sinne einmal, die bislang nicht beachteten vegetativen Rückbeziehungen etwa zur Acetonaemie der Wiederkäuer aufzudecken, die zu messen im hiesigen Institut jedoch keine Möglichkeiten bestanden und bestehen werden. Es bietet sich geradezu eine funktionelle Kette an: Gelbkörperphase — sympathikotone Stimulierung — Leistungsphase mit Laktation (vgl. z. B. Tiere mit Laktationsgelbkörper!) — Stoffwechselenergieverausgabung — sympathikotone Alkalireserveverarmung — Acidose bei evtl. gleichzeitiger Elektrolytverschiebung.

Folgende Untersuchungen erscheinen im Rahmen pharmakologischer Fragestellungen als interessant:

1. Das allgemeine Wärmemuster als Ausdruck der vegetativen Ausgangslage.
2. Das lokale Wärmemuster als Ausdruck einer speziellen Reaktion (Verbrennung, Entzündung, Schock, Wundheilung u. a. m. (Abb. 1).
3. Pyrogenteste und Fieberreaktionen bei Infektion; Hypothermie (Abb. 1 u. 2).
4. Reaktionen auf spezielle therapeutische Maßnahmen, wie Wärmebehandlung, hyperämisierende Salben und Antiphlogistica.
5. Die Messung des Wärmeverhaltens an Ganztieren als Ausdruck von Stoffwechselgrößen anstelle von — oder kompensierend zu — Respirationsversuchen (Faktoren der Tierernährung).
6. Die Messung der Bedeutung von Umweltfaktoren in der Haustier- und Versuchstierhaltung wie etwa der Wärmeverluste durch Abstrahlung im Drahtkäfig (Abb. 4).

In Verbindung mit klinischen Vorgängen würde das Zusammenspiel hormonaler Phasen mit den korrespondierenden vegetativen Stadien interessieren. Hierzu zählen z. B. die Ovulationsphase, die Corpus luteum-Phase (vgl. Basaltemperatur beim Menschen), der Eilegevorgang beim Huhn, der Ent... spartaler

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ANIMAL MODEL FOR HUMAN DISEASE	Gross Congenital Malformations	E146

Animal Model: Treatment of Various Species with a Large Dose of Vitamin A at Known Stages in Pregnancy

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Biologic Features

Large doses of vitamin A given to pregnant mammals produce many types of gross structural malformation in high incidence. This is true in the rat, mouse, golden hamster, guinea pig, and rabbit, and in limited experiments on monkeys, pigs, and dogs. The types and incidence of malformations depend on stage of pregnancy and dose, and to a lesser extent on species and strain. Doses used are hundreds of times the daily requirement. Most investigators use multiple treatments, but it is now clear that a single administration is just as effective if time and dose are chosen carefully. This model was discovered in 1953, and there are 167 papers on hypervitaminosis A teratogenesis in mammals *in vivo* (a bibliography is available from the author).

Comparisons with Human Disease

Malformations produced by hypervitaminosis A mimic human malformations of genetic, environmental and unknown causes. Malformation types can usually be divided into subtypes that vary in details of morphology and morphogenesis, and it is not possible at present to draw exact parallels between subtypes of most human malformations and experimentally produced malformations.[1] More than 70 types of malformation are produced by hypervitaminosis A. In the hamster, 18 types could be produced at more than 90% incidence, and 28 types at 10–90%.[1] Some of these are shown in Figures 1 and 2.

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Fig 1—*Left*, normal near-term hamster fetus. *Right*, hamster fetus after retinoic acid (vitamin A acid) at 22–26 somite stage shows cleft lip, digit reduction, no tail. *Middle*, 4-week-old hamster after retinoic acid at presomite stage shows *situs inversus*.

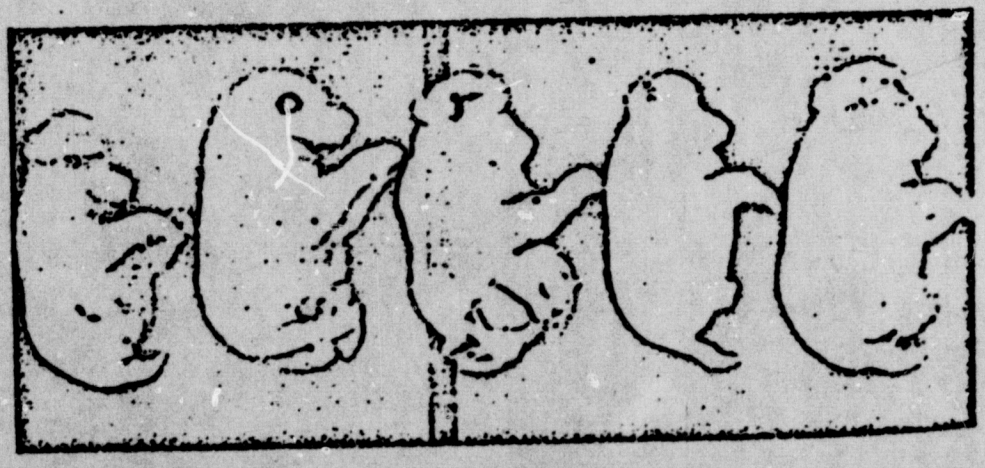

Fig 2—A litter of hamster fetuses after retinoic acid at 5–9 somite stage. Multiple malformations include sympodia, exencephaly and omphalocele.

Structures affected (and analogs of some human malformations) include the following: brain (anencephaly), spinal cord (spina bifida), face (cleft lip, cleft palate, micrognathia), eye (microphthalmia), all parts of the ear, teeth, salivary glands, aortic arch (malformations of several types), heart (ventricular septal defect), lungs, gastrointestinal tract (imperforate anus, omphalocele), liver and gallbladder, urinary system (renal "agenesis," hydronephrosis), genitalia, pituitary, thyroid, thymus, skull, vertebrae, ribs, extremities (phocomelia, digit malformations), muscles, and *situs inversus*.

Usefulness of Model

A potential use of the model is the study of sequential stages in the morphogenesis of malformations. Alternative routes of morphogenesis are readily conceivable for most malformations, and have been demonstrated for some. Sequential studies have been done on a number of hereditary malformations. There are surprisingly few studies of the morphogenesis of malformations after treatment with a teratogen. The malformations produced by hypervitaminosis A that have been sequentially studied are microphthalmia,[2] inner-ear malformations,[3] anencephaly,[4] hydronephrosis[5] and cleft palate.[6] The high incidence and known time of treatment are advantages in these studies; simultaneous effects on other organs with possible secondary effects are disadvantageous. The multiplicity of effects is an advantage in studying relationships of malformations. The biochemical basis is not known for the toxicity of vitamin A, or indeed for most of its physiologic functions, so other models are better at present for studying biochemical bases of teratogenesis. Necrosis[8] and prolongation of cell generation time[7] have been described in treated embryos, but the relationships of these and other changes of cell behavior to malformations have not been clarified. Some newborns with malformations from hypervitaminosis A can be raised but this has not been systematically explored.

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J. Ped. 5:33-43 (July) 1944

Case reports

HYPERVITAMINOSIS A AND CAROTENEMIA

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The effect on man of the ingestion of large amounts of carotene has been the subject of many articles in the past twenty years. On the other hand, knowledge of the results of overdosage with vitamin A is almost entirely confined to the effects on rats and mice. The lack of experience with hypervitaminosis in man is easy to understand, since only artificial concentrates contain sufficient vitamin A to be dangerous, and the ability to obtain these is limited. Early recognition of the possible danger of hypervitaminosis has limited the employment of excessive amounts in therapy. Moreover, the zone of safety between an adequate prophylactic dose and a dangerous dose is very large. One safeguard is lacking, that against the zeal of a person who is "sold on" vitamins. We have recently observed a case in which enthusiasm for vitamin therapy was present in a mother and eventually in her child.

REPORT OF A CASE

History.—R. B., a 3 year old boy of Jewish parentage, had appeared well up to the fall of 1938, when he was about 18 months old. At that time his appetite diminished and he seemed to be disinclined to play. Six months later (May 1939) he had a severe attack of otitis media, for which he was given sulfathiazole for two days. Two months after this, July 26, 1939, he had a tonsillectomy followed by hemorrhage, after which he received three transfusions. A blood count done after the hemorrhage showed severe anemia and 2,970,000 white cells per cubic millimeter, of which 44 per cent were neutrophils. The patient's liver and spleen were found to be enlarged, and clubbing of the fingers was noted. At this time he lost much of his hair, and that which grew back was sparse, dry and coarse.

During the next eight months, the child failed to improve, and because of the enlarging spleen and the continuing anemia he was admitted to the Harriet Lane Home for study with the tentative diagnosis of Gaucher's disease (March 1940).

Physical Examination.—When the patient entered the hospital in March 1940, his hair was sparse, dry and rather coarse, and eyebrows and fine hair over the body were lacking. The fingers and toes were slightly clubbed. He was pale and sallow, but there was no increase in pigmentation and no jaundice and the sclerae were clear. The heart and lungs showed no abnormality. The liver was felt 2 cm. below the costal margin, the edge being sharp and firm. The spleen was enlarged and firm and was palpable 3 cm. below the costal margin. The child's height was 89 cm. (about normal for his age).

This study was aided by the John Howland Memorial Fund.

From the Department of Pediatrics of the Johns Hopkins University School of Medicine and the Harriet Lane Home of the Johns Hopkins Hospital.

Laboratory Data.—Most of the laboratory data are summarized in table 1. In addition, a test of dextrose tolerance gave the following results: fasting blood sugar, one hundred cubic centimeters of blood; thirty minutes after ingestion of dextrose, one gram per kg., 152 mg.; one hour, 164 mg., two hours, 140 mg., and three hours, 111 mg. The results (in milligrams per hundred cubic centimeters of blood) in the levulose tolerance test were: fasting, 91; half-hour, 132; one hour, 131; two hours, 105, and three hours, 102. The erythrocyte sedimentation rate (corrected) was 6 mm. in one hour on one occasion and zero on two others. The bromsulphalein test of hepatic function showed no retention of the dye. Excretion of urobilin was not increased in either the stools or the urine. The Wassermann and tuberculin tests gave negative reactions.

Roentgenograms of the chest and skull showed no abnormalities, but those of the limbs revealed considerable irregularity in cortical structure. In the phalanges and metacarpals the cortex was extremely thin and the medullary cavities appeared to be "canalized." The epiphyses of the upper ends of the humeri and tibiae were mottled in appearance, and the distances between epiphyses and diaphyses were greater than normal. There were five carpal centers of ossification, indicating that skeletal development was in advance of the child's age in years.

A biopsy was done on a piece of bone, but unfortunately the tissue used was from the shaft in which no change was disclosed by roentgenographic examination; as a result we are unable to say what was the nature of the abnormal process which occurred predominantly in the upper extremities. It is, however, possible to state definitely that the marrow showed no evidence of hyperplasia, nor was there any accumulation of reticuloendothelial cells. The only abnormality was a predominance of the more immature cells of the myeloid series. It was noted that the bones became decalcified in the fixative more rapidly than usual, but there was no evidence from the biopsy of any process that might cause decalcification of the bone.

Course.—The one outstanding feature of the examination that appeared to point to a possible etiologic factor was the enormously high content of vitamin A in the serum such as would not ordinarily be encountered except four to six hours after ingestion of an excessive dose of vitamin A. On questioning the mother, it was learned that beginning at 2 to 3 months of age the child had received a teaspoonful of halibut liver oil a day (about 250,000 U. S. P. units of vitamin A) up to the present time. Moreover, he had on occasion sucked the oil directly from the bottle in undetermined amounts.

As soon as it was appreciated that the case might be one of hypervitaminosis, the child was discharged with instructions that he should not be given any extra vitamin A. Improvement was immediate. Within two months the appetite had improved, the patient had gained weight and his hair had begun to grow back normally. By the end of six months his appearance and the composition of his blood were normal and the vitamin A content of the serum was within the upper limit of normality. Certain features remained, however; the phosphatase was still elevated and the urinary findings were still depressed. For a time after he was discharged from the hospital the child showed [illegible]

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lesion and cancer, which led to a considerable though temporary increase in serum carotene and a temporary increase in serum lipids.

Two and a half years after leaving the hospital, the child was in all external appearances normal and of average height and development. He had had no illness except measles, and there was nothing in the mother's account to indicate that any pathologic change was still present. However, his liver was palpable as a firm sharp edge about 2 cm. below the costal margin; the spleen was felt as a large, firm mass occupying the upper left quadrant of the abdomen, and his fingers were still slightly clubbed. The laboratory data were essentially normal except for a slight elevation of the phosphatase content of the blood. The bones appeared normal in structure, but skeletal development was slightly in advance of the chronologic age (7 carpal centers of ossification at 5½ years of age).

In order to understand the significance of the conditions observed in this case, it will be necessary to review in considerable detail what is known concerning overdosage with vitamin A and its precursor, carotene. It has seemed best to carry out the review in the following order: (*a*) the known results of overdosage with vitamin A and carotene as determined by experiments on animals; (*b*) carotenemia as it is observed clinically, including the factors influencing the accumulation of carotene in the blood and the clinical effects of carotenemia, (*c*) hypervitaminosis, (1) the factors leading to accumulation of vitamin A in the blood and (2) the possible mechanisms the body employs to protect itself against the harmful effects of overdosage with vitamin A.

Table 1.—*Laboratory Data for Patient with Hypervitaminosis A*

Date	1/22/40	1/29/40	2/5/40	2/19/40	4/8/40	4/15/40	4/22/40	4/29/40	5/6/40	5/13/40	5/20/40
Erythrocytes, number, mm.	3,837,000	3,880,000	4,230,000	3,840,000			3,440,000		4,480,000	4,600,000	4,600,000
Hemoglobin, Gm. in 100 cc.	7.0	8.0	10.2	11.0			10.2		11.0	12.0	11.0
Leukocytes, in whole c.mm.	5,200	6,200	6,200	6,600			6,600		6,700	6,600	5,200
Neutrophils, %	62	65	65	69			69				
Lymphocytes, %	32	30	30	27			27				
Monocytes, %	6	5	5	4			4				
Eosinophils, %	0	0	0	0			0				
Basophils, %	0	0	0	0			0				
Platelets, number, mm.	180,000	180,000	180,000	180,000			180,000		180,000	180,000	180,000
Fasting blood sugar, mg. per 100 cc.	88	88	88	88			88				
Serum non-protein nitrogen, mg. per 100 cc.	25	25	25	25			25				
Serum protein, %	6.0	6.0	6.0	6.0			6.0				
Albumin, %	3.5	3.5	3.5	3.5			3.5				
Globulin, %	2.5	2.5	2.5	2.5			2.5				
Prothrombin, %	100	100	100	100			100				
Bleeding time (ear puncture), min.	2	2	2	2			2				
Coagulation time, min.	5	5	5	5			5				
Blood calcium, mg. per 100 cc.	10.0	10.0	10.0	10.0			10.0				
Blood phosphorus, mg. per 100 cc.	4.0	4.0	4.0	4.0			4.0				
Serum phosphatase, units	20.7	20.7	20.7	20.7			20.7				
Serum lipids (as 4-h. fasting, mg.)											
Total cholesterol, mg. per 100 cc.	5,200	5,200	5,200	5,200			5,200				
Free cholesterol, mg. per 100 cc.	1,300	1,300	1,300	1,300			1,300				
Cholesterol esters, mg. per 100 cc.	3,900	3,900	3,900	3,900			3,900				
Phosphatide, mg. per 100 cc.	1,300	1,300	1,300	1,300			1,300				
Neutral fat, mg. per 100 cc.	1,300	1,300	1,300	1,300			1,300				
Serum vitamin A, U. S. P. units/100 cc.	350	350	350	350			350				
Serum carotene, micrograms/100 cc.	350	350	350	350			350				

RESULTS OF OVERDOSAGE WITH VITAMIN A AND CAROTENE IN ANIMALS

As has been said above, knowledge of hypervitaminosis A is confined to the effects in animals, particularly in rats and mice, which are especially sensitive to the toxic effects of overdosage with vitamin A. Since different species vary greatly in degree of sensitivity to vitamin A and also possibly in the type of change produced by excessive amounts, one must be cautious in applying the knowledge gained by experimentation with animals to the interpretation of occurrences in the human being. There are, however, certain changes that have occurred in all the species tested, and these should form the basis for an understanding of the effects of intoxication with vitamin A. The following account will be based on the effects of excessive doses of vitamin A on the rat, since that animal has been most extensively studied.

When rats are given toxic doses of vitamin A (over 15,000 units a day), they lose weight almost immediately and may die in a week or ten days. There are certain rather constant symptoms; the hair, especially about the head, becomes unkempt and falls out and the skin becomes greasy and has a peculiar odor suggestive of hydrous wool fat. Later the eyes become sore, there is a bloody secretion from the nose and diarrhea develops.[1] These symptoms along with the extreme loss of weight and frequent loss of use of the posterior extremities provide a superficial resemblance to vitamin A deficiency. An almost constant feature is the development of multiple spontaneous fractures

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of the bones of the extremities.[2] Some investigators reported exophthalmos,[3] the cause of which is unknown; others stated specifically that they had never seen this result.[4]

Histologically two features stand out, rarefaction of the bones with extreme thinning of the cortex[5] and increased deposition of fat in the reticuloendothelial cells, especially in the Kupffer cells of the liver and in the spleen.[6] There has been considerable disagreement over the degree of accumulation of fat and the extent of the hyperplasia of the reticuloendothelial cells; some investigators reported almost none,[7] while one author likened the histologic picture to that observed in cases of Schüller-Christian disease.[8]

Other histologic changes were noted by various authors, some of which may be of considerable significance if confirmed. Some authors, for instance, found evidence of increased activity of the thyroid gland[9]; one stressed increase in the basophilic cells of the anterior lobe of the hypophysis,[9] and hypertrophy of the island tissue of the pancreas was reported by another.[9]

Although the anatomic studies have usually been made on severely intoxicated animals, certain of the changes, especially those in the reticuloendothelial cells, are known to occur also in animals less severely poisoned. This fact indicates that such changes are the result not of a general intoxication but of a process more specifically associated with excess of vitamin A. Investigations of the relationship of overdosage with vitamin A to fat metabolism tend to confirm this suggestion. Since this subject has recently been reviewed,[9] it need only be touched on here.

When vitamin A in large but nontoxic daily doses was given to rats, guinea pigs or rabbits, a rise in cholesterol and in total lipids of the serum occurred.[10] This rise was only temporary, however, and tended to disappear after a time, even while the large doses of vitamin A were being given.[10] The same effect was observed in human beings[11] but not in dogs.[12] In rats previous deficiency intensified and prolonged the response,[3] and a similar reaction was seen after pneumonia in infants receiving vitamin A.[13] Apart from this lipid reaction, the effect of vitamin A on physiologic processes has been little studied. No effect was observed on the formation of blood in animals.[14] The serum calcium and phosphorus were not affected, though there was an increase in excretion of calcium, which was attributed to "decalcification" of the bones.[15] The basal metabolic rate was decreased.[16] An observation of considerable significance, if confirmed, was that function of the liver was at first improved and then depressed by excessive vitamin A.[17] All authors are agreed on the fact that recovery is prompt when the excessive intake of vitamin A is discontinued.

In contrast to the harmful results of overdosage with vitamin A, toxic effects have not been seen in animals after ingestion of excessive amounts of carotene; the animals have not lost weight or died and have not shown any of the outward manifestations of hypervitaminosis.[18] The changes in the metabolism of fat and the histologic changes in the reticuloendothelial system,[6] especially the increase in the storage of fat, are the same after the ingestion of carotene

2. (*a*) Bumskov and Seemann.[1d] (*b*) Davies and Moore.[1e] (*c*) Baumann and Moore.[1f] (*d*) Collazo, J. A., and Rodriguez, J. S.: Klin. Wchnschr. 12:1769, 1933. (*e*) Strauss, K., and Ziegl, B.: Beitr. z. path. Anat. u. z. allg. Path. 94:345, 1934. (*f*) Weslow, W.; Wroeski, B.; Wroblewski, A., and Wroblewski, B.: Klin. Wchnschr. 17:777, 1938.

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11. (*a*) Josephs.[9] (*b*) Wendt.[10c]

12. (*a*) Wendt.[10c] (*b*) Josue, H.: Deutsche med. Wchnschr. 60:573, 1934. (*c*) Lasch, P.: Klin. Wchnschr. 13:1934, 1934.

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17. (*a*) Moll and others.[1b] (*b*) Davies and Moore.[1e] (*c*) Chevallier, A.; Cornil, L. [illegible] Compt. rend. Soc. de biol. 113:574, [illegible] and Reil, L.: ibid. 119:577, 1935.

The most obvious reasons for the less pronounced effects with carotene are: (1) carotene is less well absorbed than vitamin A; (2) the effect of carotene is seen only after conversion to vitamin A and the time taken for this conversion would prevent the flooding of the body with the active vitamin which is necessary for the production of toxic effects. This subject will be more fully discussed in the section devoted to the body's defense against hypervitaminosis.

CLINICAL CAROTENEMIA

Factors Influencing the Carotene Level of the Blood.—1. Diet: Recognition of the primary importance of diet in carotenemia came as the result of the work of Palmer[19] and van den Bergh[20] and of a large number of clinical observations, most of them on children and persons with diabetes. These studies revealed correlations of xanthosis of the skin with increased content of lipochrome[21] in the blood and with diets rich in lipochromes (carotenuria).[22] Carrots are the primary food associated with carotenemia; also important are squash,[23a] oranges[23b] and egg yolk[23c] (egg yolk supplies xanthophyll rather than carotene). Xanthosis of dietary origin is most common in the late summer,[24a] and a number of observers have noted that the carotene of the blood is normally at a higher level at this time of the year.[24b] In the cases reported in pediatric clinics, young infants appeared to be spared; the condition is observed only in later infancy and early childhood.[24c] It is generally recognized that carotenemia and xanthosis are slow to develop, and relatively slow to recede after the high intake of carotene is discontinued.[25a] Not every one reacts in the same way to the same diet, and it has been observed that some persons who acquire xanthosis easily do so on a surprisingly small extra amount of carotene.[25b] Moreover, the reactions of the same person may vary; it has been noted that a carotene-rich diet may cause xanthosis at first but that the yellow color may later disappear not to return during continuance of the diet.[25c]

2. Level of Serum Lipids: The suggestion was made early that the serum lipids might have something to do with the development of carotenemia. The conditions other than ingestion of diets high in carotenoids under which carotenemia occurs in human beings are in general those associated with hyperlipemia—diabetes, nephrosis[26] and hypothyroidism.[27a] In cases of diabetes of the type in which the serum lipids are increased there is also a tendency for carotenemia to develop.[27b] Rabinowitch[27c] reported that these patients with the highest levels of serum carotene tended in general to have the highest levels of lipid. If a large enough number of cases is studied to obtain the extreme variations in values which are encountered only under pathologic conditions, it can be shown that a correlation does exist.[28a] However, the lack of demonstrable correlation in small series and under normal conditions has led several observers to deny that the lipids have any significance in carotenemia.[28b]

In a recent study, it was found that during and after pneumonia the levels of carotene and of lipid could be correlated when account was taken of the ingestion of carotenoids and the time required after ingestion for accumulation of the carotenoids in the blood. When carotene was given by mouth the rate of accumulation in the blood stream depended in general on the level of lipid during the period of ingestion.[28c] In a recent study of hypothyroidism the values of serum carotene were found to be dependent on those of the serum lipid.[28d] A close relationship between carotene and cholesterol has been stressed, and it has been claimed that the yellow color of the nodules present in xanthoma is due to their content of carotene.[28e]

3. Other Factors: The fact that when carotenoids are removed from the diet the carotene of the serum falls to an extremely low level suggests that the stores of carotene in the fat depots are only to a minimal extent available for maintenance of the level in the blood. Moreover, it has been found that thin people have a higher concentration of carotene in the fatty tissue than well nourished persons,[29a] which indicates that even when fat is mobilized from depots in the tissues, carotene remains behind. The fate of the carotene which disappears from the blood is not entirely known. Some of it is evidently deposited in the fatty tissues. A large part is removed from the circulation in the liver, where it undergoes conversion to vitamin A. Some of it is undoubtedly oxidized. Whether or not it has any function other than as a source of vitamin A is unknown.

The increase in the activity of the reticuloendothelial cells after the ingestion of carotene may explain why the high initial carotenemia tends to disappear later; the rapidity with which removal is accomplished is at first exceeded by the rate of intake but later increases to take care of the excess carotene. It has been suggested that hypothyroidism[30] and diabetes interfere specifically with the conversion of carotene to vitamin A, but it is hard to see how this would lead to accumulation of carotene in the blood unless the mechanism of removal were also impaired. Several investigators have advanced the hypothesis that failure of oxidation of carotene is the determining factor, especially in diabetes and hypothyroidism.[31] Until more is known concerning the part that oxidative processes play in the removal of carotene from the blood in the living organism, and not merely in vitro, this hypothesis can hardly be proved or disproved.

Carotenemia has been noted among Europeans living in the tropics, and Castellani and Chalmers[32] mentioned a condition which they called ochrodermatosis, which occurred only at sea level and disappeared when the patients were removed to higher altitudes. The diet was not mentioned. Sequeira[33] saw what he considered a similar case in Africa apparently not dependent on diet and without hypercholesteremia. Improvement occurred only after the patients were given small amounts of thyroid. Boumis and Levinson[34] reported carotenemia in a group of patients with chronic malaria who had been adequately treated.

Effects of Carotenemia.—Xanthosis of Carotenemia has been considered completely harmless, its only symptom being the disappearance of the characteristic yellow color of the skin which generally disappears as soon as the responsible conditions have been corrected. Usually the yellow color varies with the level of carotene in the blood, but a close parallelism is not always present. A striking example to the general rule is the absence of xanthosis in persons with carotenemia with myxedema.

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20. van den Bergh, H.: Muller, P., and Broekmeyer, J.: Nederl. tijdschr. v. geneesk. 2:127, 1920.

21. The terminology in this field is confusing. "Lipochrome" refers only to a colored substance associated with fat and is the older term. The early recognition and the importance of carotene among the lipochromes has led to the general use of the term carotenoids to designate this class of substances, all the members of which have similar chemical structures. In most clinical work "carotene" is used to designate anything that gives a yellow color in the purified benzine (petroleum ether) layer above an alcohol-water mixture. This is an incorrect use of the term but does no harm as long as the fact is recognized. "Carotenemia" is a term introduced by Hess and Meyers to include the entire clinical picture of yellow skin and increase of carotene in the blood; as such it has been widely accepted. It must be recognized, however, that the yellow color of the skin is not due to the carotene content of the blood, and, although there is a relationship, it is not always a close one. There is now a tendency to distinguish between "carotenemia" (excessive carotene in the blood) and "xanthosis cutis" (yellowness of the skin). As in the case of the faulty use of "carotene," the use of "carotenemia" to cover the entire syndrome does no harm, but it is well to recognize the possibilities for confusion.

22. (a) Hess, A. F., and Myers, V. C.: Carotinemia: New Clinical Picture, J. A. M. A. 73:1743 (Dec. 6) 1919. (b) Kaupe, W.: Munchen. med. Wchnschr. 66: 330, 1919. (c) Klose, E.: Ibid. 66:419, 1919. (d) Stoeltzner, W.: Ibid. 66:419, 1919. (e) Rybiczek, P.: Jahrb. f. Kinderh. 91:225, 1921. (f) Kohn, R.: Ztschr. f. d. ges. exper. Med. 36:147, 1923. (g) Hashimoto, H.: Carotinoid Pigmentation of Skin Resulting from Vegetarian Diet, J. A. M. A. 76:1111 (April 15) 1922. (h) Miyake, I.: Arch. f. Dermat. u. Syph. 147:194, 1924. (i) Greene, C. H., and Blackford, L. M.: M. Clin. North America 10:733, 1926. (j) von Drigalski, W.: Ztschr. f. Vitaminforsch. 3:37, 1934. (k) Clausen, S. W., and McCord, A. B.: J. Pediat. 13:635, 1938.

23. (a) Miyake:[redacted] (b) Josephs, H. W.: Personal observation.

24. (a) Stoeltzner:[redacted] (b) Clausen and McCord:[redacted]

25. (a) Clausen and McCord:[redacted] (b) Catel, W.: Monatschr. f. Kinderh. 73:316, 1938. (c) Kimble, M. S.: J. Lab. & Clin. Med. 23:1055, 1938.

26. (a) Kaupe:[redacted] (b) Stoeltzner:[redacted] (c) Kohn:[redacted]

27. (a) Clausen and McCord:[redacted] (b) Kaufmann, F., and von Drigalski, W.: Klin. Wchnschr. 12:300, 1933. (c) Heymann, W.: Carotinemia in Diabetes, J. A. M. A. 106:2090 (June 13) 1936.

28. (a) Klose:[redacted] (b) Ender, F.: Klin. Wchnschr. 53:859, 1916.

29. (a) Wendt:[redacted] (b) Clausen and McCord:[redacted] (c) Josephs, H. W.: Personal observation.

30. (a) Wendt:[redacted] (b) Ender:[redacted] (c) Isbell, M.: Presse méd. 33:17, 1925. (d) Rabinowitch, I. M.: Canad. M. A. J. 18:337, 1928; (e) Carotinemia and Diabetes: Relationship Between Sugar, Cholesterol and Carotin Contents of Blood Plasma, Arch. Int. Med. 45:536 (April) 1930. (f) Barbuio, N., and von Querner, P.: Wien. Arch. f. inn. Med. 30:279, 1937.

31. Josephs, H. W.: Bull. Johns Hopkins Hosp. 63: 112, 1939.

32. (a) Ralli, Pariente, Brandaleone and Davidson:[redacted] (b) Berger, M., and Richards, A.: Deutsche med. Wchnschr. 63:134, 1919. (c) Ralli, E. P.: Brandaleone, H., and Mandelbaum, T.: J. Lab. & Clin. Med. 20:1266, 1935.

33. Josephs, H. W.: To be published.

34. (a) Thomson, J. G.: Ztschr. f. d. ges. exper. Med. 92:692, 1934. (b) Bamfield, H.: Klin. Wchnschr. 13:36, 1934.

35. Feodd, H., and Holdsworth, L. R.: Ztschr. f. d. ges. exper. Med. 92:53, 1933.

36. (a) Ralli, Pariente, Brandaleone and Davidson:[redacted] (b) Ralli, Brandaleone and Mandelbaum:[redacted]

37. (a) Heymann:[redacted] (b) Stevens, H. S.: J. Lab. & Clin. 1:146, 1915. (c) Rosenau, F., and Levinson: Ztschr. f. Vitaminforsch. 3:12, 1934.

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39. Sequeira, J. H.: Brit. J. Dermat. 43:1.

(Clausen and McCord[38] and personal observations). Histologic examination shows that the carotene is found mostly in the superficial horny layer of the skin and that its concentration becomes less the deeper one goes.[39] The fact that it is present in sweat and sebaceous material has led to the hypothesis that its presence in the skin is dependent on this excretion and the subsequent rubbing of the carotene into the horny layer. Its predominant occurrence in those areas in which the horny layer is particularly thick or in which sweating is most marked (palms and soles, forehead, nasolabial folds, axillas and groins) would tend to bear out this theory.

2. Increased Serum Lipids: Anderson and Soley[40] noted an increase in serum lipids and pronounced fall in basal metabolic rate in several California farmers who had eaten vegetables in large amounts. The liver was enlarged in 4 of the 9 patients. An increase in serum lipid was noted by two other observers[40] but, in general, little attention has been paid to the blood lipids in carotenemia.

3. Harmful Effects: Some recent work throws doubt on the generally accepted harmlessness of carotenemia. Sequeira[41] reported weakness, loss of weight and low blood pressure. He was speaking, however, of cases observed in the tropics in which diet was apparently not a factor; hence it is possible that the carotenemia was secondary to some underlying factor responsible for the whole condition. Anderson and Soley reported that the liver was enlarged in about half of their patients and that the removal of rose bengal from the blood was slower than normal.

A more certain example of harmfulness is furnished by a case recently reported by Henschen.[42] A woman of 49 acquired a pica-like craving for carrots during an attempt to cure "anemia" with a vegetable diet. She ate 2 to 3 kilograms a month (about 2 pounds [0.9 Kg.] a day), mostly raw, for six months, and a generalized xanthoiris cutis developed. She also complained of paresthesias of the hands and feet. She was thin, pale, rather easily fatigued and subject to dyspnea. The liver and spleen were enlarged. The yellow color was general over the body, but the scleras were clear. Examination of the blood gave the following data: The hemoglobin content was 57 per cent. Erythrocytes numbered 3,400,000 per cubic millimeter and leukocytes 5,300, with neutrophils 62 per cent, lymphocytes 28 per cent and monocytes 4 per cent. There was poor clot formation, but no estimation of the number of platelets was made. There was 0.317 mg. of carotene per hundred cubic centimeters of serum (normal 0.07 to 0.19). Serum xanthophyll was not increased. When carrots were removed from her diet, the patient slowly improved, though the number of white cells remained low. Later cataracts developed.

Reports of Earlier Cases of Dietary Carotenemia.—In the records of the Johns Hopkins Hospital there are 6 cases of carotenemia in which the diet alone either was or might have been responsible. This series is exclusive of cases of carotenemia occurring in the course of diabetes or nephrosis or of hypothyroidism, in which the low thyroid function is definitely the primary factor. They are included at this point because they have a bearing on the discussion of hypervitaminosis and because they confirm the hypothesis that carotenemia may not be as harmless as heretofore pictured.

Case 1.—The patient was a child of 16 months, who had recently come from California, where she had been indulged in oranges, the only source of carotene that she could be ascertained to have received in significant amount. She recovered promptly and at no time did untoward symptoms develop.

Case 2.—The serum of this patient, also a child, was received for diagnosis. All that I can ascertain is that no harm resulted from the carotenemia and that the clinical diagnosis was made from the yellow color of the skin. It is unusual to see xanthosis cutis with the serum carotene as low as it was in this case.

Case 3.—Carotenemia was diagnosed in a well-to-do asthmatic man who enjoyed vegetables in large quantities. No special studies were made, and the case is included only as one in which the patient was not harmed by the carotenemia.

Case 4.—A 38 year old clergyman had as his only complaints yellowness of the skin and loss of weight. He had been supplementing his diet with carrots and carrot juice for about seven years. When carrots were removed from his diet, he recovered rapidly.

Case 5.—This patient, a colored farmer who had lived largely on vegetables, especially spinach, was extremely undernourished. Low blood pressure, constipation and extreme muscular weakness led to a first impression of hypopituitary cachexia (Simmonds's disease). Later, hypothyroidism was suggested on the basis of the high serum cholesterol and low basal metabolic rate. On a diet of high caloric value he improved extraordinarily rapidly.

Case 6.—A well-to-do woman of 48, because of ingrained idiosyncrasies to meat, eggs, milk and starchy foods, had lived largely on vegetables and fruits for a number of years. In addition to having carotenemia, she was markedly underweight, with low blood pressure and asthenia. Hypothyroidism was diagnosed on two occasions when she was in the hospital. She was greatly improved by a diet high in calories, given in the hospital.

The patients in the first 3 of these cases were symptomless and entirely unharmed by the carotenemia. In case 1, however, the serum lipids were well above the normal. The last 2 cases considered by themselves would be hard to evaluate; in case 5 the extremely inadequate diet might have caused the entire clinical picture, and in case 6 the impression of hypothyroidism was particularly strong and in addition the diet was inadequate. Certainly the cases in which there is evidence of harm were those in which the patient had taken the carotene-containing foods for a long time or had lived largely on them. Case 4 is the link connecting the cases of innocuous carotenemia with those in which harm has resulted; in this case there is no doubt of the primary position of the carotenemia, and at the same time the patient showed loss of weight, asthenia, high blood lipids and cholesterol and a low basal metabolic rate.

From these cases plus those described by Anderson and Soley, of carotenemia in California farmers,[40] one may form a picture of the effects of carotenemia. Loss of weight is usual, but it is not possible to be certain to what extent this is the direct result of carotenemia and to what extent the result of the concurrent inadequacy of the diet. The same is true of muscular weakness. Hypotension is even more difficult to evaluate. It was not mentioned by Anderson and Soley. In case 6 of the series just described the low blood pressure antedated the abnormal diet; in case 5 the extreme inadequacy of the diet may have caused the low blood pressure, in case 4 the blood pressure was not very low. The high values for blood lipids and cholesterol and the low basal metabolic rate definitely part of the picture of carotenemia occurring as they did in Anderson and Soley's cases as well as in 3 of the 4 cases here in which the lipids were determined. A tendency to leukopenia also appears to be a characteristic, but one that may not be always present, as in the series I have reported it occurred in only 3 cases with symptoms (4 and 5), as it was not present in Henschen's case. Anderson and Soley merely stated that the blood was normal, not reporting the actual counts.

Perhaps the most convincing aspect in the relationship of carotenemia to hypervitaminosis A

Table 2.—*Laboratory Data for Patients with Carotenemia*

Case No.	Age, Sex	Source of Carotene	Date	Serum Carotene, Micrograms per 100 Cc.	Serum Vitamin A, U. S. P. Units per 100 Cc.	Serum Lipids, Mg. per 100 Cc.	Serum Cholesterol, Mg. per 100 Cc.	Blood Hemoglobin, Gm. per 100 Cc.	Loss of Weight	Weakness	Hypotension	Leukopenia, Number per Cu. Mm.
1	16 mo. F	Oranges	6/6/33	400	60	1,200	—	—	0	0	—	—
2	6 yr. F	Carrots	Jan. 1933	800	90	600	—	—	0	0	—	—
3	37 yr. M	Carrots	Oct. 1933	—	—	—	—	—	0	0	—	5,000
4	38 yr. M	Carrots and carrot juice for 7 years	6/32 3/33 12/33	400 500 550	60 100 100	1,400 700 700	400 — —	—60 — —	+	+	80/60	4,200
5	35 yr. M	Vegetables, especially spinach, principal source of food for 7 years	12/33	200	—	1,200	400	—60	++	++	++, 70/50	6,000
6	47 yr. F	Vegetables and fruit principal source of food for 4 years	—	—	—	—	Elevated	—60	++	++	+	4,000

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48. (a) Hashimoto:[39] (b) Miyahi:[39] (c) Ansel, cited by Zechmeister, L.: Ergebn. d. Physiol. 39:117, 1937.

41. Anderson, E. H., and Soley, M. H.: Am. J. M. Sc. 193:313, 1937.

42. (a) Kuhn:[39] (b) Lian, C.; Abaza, A., and Sautier, R.: Bull. et mém. Soc. méd. d. hôp. de Paris 51:831, 1935.

43. Henschen, C.: Schweiz. med. Wchnschr. 71:331, 1941.

tions carotene must be ingested in excessive amount for a long time or must form the major part of the diet to the exclusion of other constituents in order to be harmful.

CLINICAL HYPERVITAMINOSIS

Factors Influencing Vitamin A of the Blood.—Little is known of the factors leading to the increase of vitamin A in the serum, and that little has come principally from experimentation on animals.

1. Diet: Increasing the dietary intake of vitamin A beyond a certain optimum will increase the amount stored, but it is usually not possible to push the level of vitamin A in the blood above what might be called a normal maximum, except for a few hours after administration of a large dose. A child of 4 years who was given percomorph liver oil in large doses for resistant rickets received about 120,000 U. S. P. units of vitamin A every day for a month with no more than a minimal effect on her serum vitamin A, determined twenty-four hours after the last dose. Two infants were given 300,000 U. S. P. units of vitamin A a day for several weeks. There was a slight temporary rise in vitamin A in the blood, lasting about a week. Likewise, in rats ingestion of 2,500 U. S. P. units a day raised the level of vitamin A from 1 unit per cubic centimeter of serum to about 2 units, and, although a large amount was stored in the liver, the serum vitamin A fell to nearly its former level within two or three days after the high ingestion of the vitamin was discontinued.[44]

2. Level of Serum Lipids: The conditions in which hyperlipemia occurs tend to be associated with increases in vitamin A as well as with carotenemia. Also, as in the case of carotenemia, the relationship is of a general nature and one must utilize pathologic extremes to be able to demonstrate it.[45] An important difference lies in the far more rapid removal of excessive vitamin A than of carotene from the blood. The postabsorptive curve of vitamin A is influenced by the level of serum lipid just as is that of carotene,[46] but the specific removal of vitamin A in the liver effectively prevents prolonged accumulation in the blood, while the slower removal of carotene permits an accumulation which is also aided by the relatively higher solubility of the latter substance in the blood lipids. It seems likely also that the solubility in lipids is a less important factor in the case of vitamin A than of carotene. If vitamin A and lipids tend to vary together, it is because they are subject to similar influences.[47]

The highest values for vitamin A seen in over 700 cases did not exceed 2.5 units per cubic centimeter except immediately after ingestion, even though the series included some cases with high levels of lipid (cases of nephrosis and 1 of myxedema). Following pneumonia there was a tendency for hyperlipemia to develop in some of the children observed; under these circumstances the vitamin A might temporarily reach a value of 3.5 units per cubic centimeter of serum (patients not receiving supplementary vitamin A). These levels were the highest seen with the exception of those in the case of vitaminosis reported here.

Protection Against Hypervitaminosis.—A factor of safety for the animals that rely on carotene for their source of vitamin A is the relative harmlessness of carotene. Also any damage which it does cause is apparently not permanent, and rapid and complete recovery is to be expected as soon as the excessive intake of carotene is stopped.

The facts just reviewed point to the existence of a mechanism for the maintenance of the level of vitamin A in the blood within certain limits. It seems highly significant that this mechanism exists in the case of the vitamin, which can produce toxic effects, and not in the case of its precursor, carotene, which appears to be relatively harmless. It is interesting that the dog, which apparently lacks this mechanism for the limitation of the level of serum vitamin A (personal observation), is the one animal thus far studied in which none of the toxic effects from vitamin A have been elicited.[48]

Another protective mechanism is the storage of vitamin A in the liver, where it appears to be harmless. It is not the total amount of vitamin in the body that determines the presence of toxic symptoms but the ingestion of amounts large enough to overwhelm the ability of the liver to remove it from the circulation.[49] Seemingly it is possible to push the storage in the liver without limit, and no symptoms of intoxication are produced unless the daily dose is raised above the "toxic" limit. When vitamin A or carotene is given intravenously the excess is removed with great rapidity.[50] In this removal the cells of the reticuloendothelial system play a primary role, particularly the Kupffer cells of the liver. This has been shown by flavine-fluorescence microscopy[51] as well as by "blockade" experiments.[52] The increase in activity of these cells under the influence of overdosage with vitamin A may therefore be looked on as a factor in the defense against hypervitaminosis.

When excessive vitamin A is given to rats over a period of time, a rise in the level of serum lipid occurs, which, however, is temporary. This has been taken as evidence that one of the fundamental effects of vitamin A is on the metabolism of lipids, but that ordinarily the effect is adequately and promptly compensated for. When the vitamin is suddenly introduced in large amounts the compensatory process is temporarily overcome and a rise in blood lipid occurs. It has been suggested that this compensatory process involves increased activity of the thyroid gland.[53] Support for this idea comes from the demonstration of antagonism between vitamin A and thyroxin.[54] The continuance of the high content of lipid in the serum in the cases of carotenemia cited in this paper suggests that this compensatory factor may be more effective in the rat than in man.

COMMENT ON THE CASE

From this review of reports of experimental and clinical carotenemia and hypervitaminosis A, one obtains some insight into the significance of certain pathologic changes in the case which is reported. However, since final proof of the mechanisms involved is lacking, the interpretations which follow must be looked on as suggestions rather than as demonstrations of the manner in which excessive vitamin A acts.

Abnormal Appetite.—Whether or not it is justifiable to label as "abnormal" a liking for an article of food which most people would not eat by choice, there is no doubt that the child's liking for halibut liver oil was a factor in the case which is reported. It is interesting that this desire for the oil was replaced by a desire for butter and carrots after the administration of the oil was discontinued, and that as the patient improved clinically he lost all such desires. Henschen's patient with carotenemia had developed such an appetite for carrots that she was impelled to search garbage cans to satisfy her craving. Two of Hashimoto's patients among Japanese peasants had an abnormal appetite for squash, the source of their carotene. Clausen and McCoord mentioned a case in which the patient had an abnormal craving for carrots; the carotene in this case was the highest in the series. These examples are cited to show that abnormal appetite for carotene-containing foods may occur.

It is possible that the appetite existed first and was primarily responsible for the large intake, but it seems more probable that the interest in halibut liver oil was begun for economic or other reasons and that the abnormal appetite developed subsequently. Desire for some particular dietary constituent infrequently results from the necessity of correcting a deficiency or some other condition, for example, the craving for salt in persons with adrenal insufficiency. It is conceivable that excessive vitamin A or carotene taken at first through economic necessity or real might give rise to changes that would create or increase the desire for the material that caused the changes. The change in desire from halibut liver oil to carrots and butter in our patient when use of the oil was stopped suggests that this was the case. It will be noted from table 1 that after the patient was discharged from the hospital the carotene in the serum rose for a short time to a definitely abnormal level, which confirms the history of increased intake of carotene.

Hepatomegaly and Splenomegaly.—The original impression of Gaucher's disease was suggested by the presence of a large liver and spleen together with anemia of the hyperplastic type. The roentgenograms of the bones were not indicative of this condition except that the cortex in the metacarpals and phalanges suggested the presence of a process replacing normal bone with pathologic tissue. The increased deposition of fat in animals subjected to intoxication with vitamin A suggests the possibility that such storage may have occurred in our patient. However, we have no direct evidence of this, nor any reticuloendothelial proliferation, as in the bone marrow, though such a proliferation may account for the enlargement of the liver and spleen. The improvement of the patient on ingestion of excessive vitamin A was not conclusive evidence that vitamin A intoxication was primarily responsible for the clinical picture. It may be pointed out in confirmation that Herter's original patient also had hepatomegaly and splenomegaly with a hyperplastic type of anemia, and that the cases of carotenemia which I summarized in patients who had any symptoms tended to show leukopenia and a slight reduction in the number of red cells.

The idea that vitamin A and carotene are capable, under conditions that lead to accumulation in the blood, of causing a disturbance

44. Josephs, H. W.: Bull. Johns Hopkins Hosp. 71: 233, 1942.

45. Josephs, H. W.: Bull. Johns Hopkins Hosp. 71: 233, 1942.

46. (a) Davies and Moore:[39] (b) Bergeld, I.: Ztschr. f. Vitaminforsch. 7:113, 1938.

47. (a) Drummond, J. C.; Gilding, H. P., and McWalter, R. J.: J. Physiol. 82:7P, 1934. (b) Gronwall, H., and Sturmark, L.: Acta med. Scandinav. 101:133, 1939.

48. Popper, H., and Brenner, S.: J. Nutrition 23: 431, 1942.

49. Lauch, F., and Roller, D.: Klin. Wchnschr. 18: 1435, 1939.

50. Wenk, H.: Deutsche med. Wchnschr. 62:1213, 1936.

storage of lipids with certain features in common with the changes which occur in xanthomatosis, Gaucher's disease or Niemann-Pick disease is an attractive one. However, the reported effect of vitamin A on reticuloendothelial proliferation in animals has not yet been thoroughly confirmed, nor has it been shown that the splenomegaly or hepatomegaly in clinical cases is actually due to increase in the storage of lipids.

Increased Vitamin A in Serum.—The vitamin A of the blood of our patient when first seen was at a level which has otherwise been encountered only at the height of the postabsorptive curve, four to six hours after a relatively large dose. Not only that, but it remained at a high level after all excess ingestion of vitamin A had been stopped and only slowly returned to normal over a period of six months. As stated previously, attempts to cause a rise in serum vitamin A in other patients to more than a limited extent or over more than a limited time have proved unsuccessful. While this paper was in preparation a child of 8 months was brought to the outpatient department after receiving 3 teaspoons of percomorph liver oil a day during a period of four months (corresponding to about 500,000 U. S. P. units of vitamin A per day). The vitamin A of the serum was 110 U. S. P. units per hundred cubic centimeters and the total lipid 730 mg. per hundred cubic centimeters, both normal values. This case exemplifies the efficiency of the mechanism by which the constancy of the blood vitamin A is maintained and at the same time indicates that this mechanism in the patient whose case is reported here was seriously impaired.

In the discussion of the body's protection against hypervitaminosis the role played by the reticuloendothelial cells in removing vitamin A and carotene from the blood was cited. If, as has been suggested, the cells of the reticuloendothelial system are made more active by an overdose of vitamin A the vitamin would be more, not less, effectively removed from the blood. The fact that in the case under discussion the vitamin was less effectively removed indicates either that the child had some defect in his reticuloendothelial response or else that intense, prolonged overdosage is capable of injuring this response. The only work that I could find bearing on this point is that of Ikegaki,[10] who found that in early stages of overdosage with vitamin A liver function increased, whereas later it decreased; the functions dealing with removal of dye from the blood stream and with detoxification were particularly affected. In our patient, bromsulphalein was removed normally but the serum bilirubin was consistently somewhat raised (1.6 mg. per hundred cubic centimeters). In Anderson and Soley's cases of carotenemia, 5 of the 8 patients tested showed impairment of the ability of the liver to remove rose bengal from the blood.

A second possibility in this case is that the limit of the liver's ability to store vitamin A was exceeded. While little is known of the capacity of the human liver, work on rats shows that when storage of vitamin A has been pushed to a high point the vitamin disappears with great rapidity when excessive intake is discontinued, supposedly by oxidation or some other form of destruction. Whether or not prolonged administration of vitamin A could impair this mechanism for getting rid of amounts in excess of the storage capacity is not known. As I have pointed out, however, excessive storage has little influence on the level in the blood, so that it would be difficult to explain the continuance in this patient of a high level over a prolonged period after the intake of vitamin A was discontinued, especially since the total amount in circulation is only a minute fraction of the amount in storage.

Increased Level of Serum Lipids.—The increase in lipid in the blood in the patient under discussion was definite though not excessive. (The normal range is approximately 550 to 750 mg. per hundred cubic centimeters, though higher may be encountered in otherwise normal persons.) The gradual fall after excessive intake of vitamin A was stopped leaves no doubt regarding the causation. The level of carotene in the patient's serum was not excessively high except on one occasion, as previously mentioned, just after his return home, when he had a craving for carrots and butter. It may be noted that on this occasion the content of lipids also increased slightly. A rise in blood lipids appears to be a significant part of the picture of hypervitaminosis A as well as of carotenemia. The cholesterol also takes part in the rise of lipids but in some cases, as in those reported by Anderson and Soley, the increase is not correspondingly great. The basal metabolic rate was not determined in the patient discussed with hypervitaminosis A, but it was decreased in most of my patients with carotenemia. In fact, the picture of carotenemia resembles that of hypothyroidism to such an extent that a distinction may be difficult. Only the definite association of the condition with a vegetable diet and its disappearance as soon as the source of carotene was removed lead to a correct diagnosis of carotenemia. The explanation for the similarity between the two conditions may lie in the vitamin A thyroid antagonism to which reference was made previously, in which case the symptoms of hypothyroidism in carotenemia would be due to the presence of an excess of thyroid antagonist and not to an actual diminution in the activity of the thyroid gland.

It was pointed out previously that the rise in lipids which occurs in animals subjected to continued excessive doses of vitamin A or carotene was a temporary phenomenon and that the return to normal levels was evidence of the development of a compensatory process. Wendt suggested that the compensation might involve an increase in thyroid activity.[10] I have suggested that the continuance of the high level of lipids in the patient reported on here might also indicate that the "compensatory" process is less effective in man than in rats. The fact that the dose required to elicit the lipid response in man is relatively far smaller than that for rats[11] points in the same direction. If, as suggested, increased activity of the thyroid supplies the "compensatory" process, its relative failure in man might explain both the persistence of the high levels of serum lipid and the symptoms of hypothyroidism.

Skeletal Abnormalities.—The skeletal changes which occurred are difficult to evaluate, and the biopsy was of no aid. The speed of decalcification was in line with the observation that in animals decalcification of bones is one of the most constant effects of hypervitaminosis. The most outstanding features in the roentgenograms of the patient were the evidences of a more rapid epiphysial development, the irregularities, the apparent stippled effect of the epiphysial centers, the increased distance between epiphysis and diaphysis and the advanced development of carpal centers of ossification. Even two and a half years after the removal of excessive vitamin A the carpal centers were in advance of the patient's chronologic age. The child, however, has not grown unduly and at present is no more than at the upper limit of normal stature for his age. It may be mentioned that Wolbach and Bessey[12] in a recent review stated the opinion that vitamin A acts to increase the rate of development of bone; however, they gave none of the evidence on which the opinion was based.

Associated Abnormalities.—Four other abnormal conditions present in this case are worth noting. (*a*) The rise in serum phosphatase depends on the activity of processes which also give rise to changes in the bones, and it is to be considered in relation to these. Phosphatase is also increased in diseases of the liver, and, as has been pointed out, there is evidence of hepatic damage in this case. (*b*) The low level of serum protein, especially of the globulin fraction, is probably of considerable significance, but it cannot be evaluated in the present state of knowledge. (*c*) Sparse, coarse hair [illegible] a prominent characteristic of the clinical picture. Loss of hair by rats subjected to vitamin A intoxication has been a prominent feature of some observations. In the patient, the return of hair of normal texture and distribution was almost the first sign of improvement. (*d*) Clubbing of the fingers was a striking feature of the clinical picture when the child was first seen. It was still present though less prominent after two and a half years. Its significance is not known, but it may possibly indicate damage to the liver, since clubbing of the fingers and toes is not infrequently observed in cirrhosis in children.

The question of complete recovery of the patient in the case reported is still open. Clinically the child is well and has remained so during the past two years. The only causes for concern are the continued presence of splenomegaly and a less degree of hepatomegaly and the slight advance in skeletal development. In [illegible] case splenomegaly was slow to disappear, leukopenia persisted for at least a year. Because of the magnitude and the duration (three years) of the intake of vitamin A it would be surprising if some permanent change had not resulted. My fear is not so much that there may be some progressive process still active as that there may have been some scarring of the liver that will give rise to trouble.

SUMMARY

Severe hypervitaminosis A occurred in a child of 3 years who had received about 500,000 U. S. P. units of vitamin A daily since the age of about 3 months of age. The condition was characterized by hepatomegaly, splenomegaly, hypoplastic anemia, leukopenia, increased serum vitamin A, increased serum lipids, advanced skeletal development, clubbing of the fingers and sparse coarse hair; it was accompanied with a ravenous appetite for halibut liver oil, the source of the vitamin. Most of the symptoms cleared up when the excess vitamin A was removed from the diet.

Experimental and clinical observations support the existence of a mechanism for the maintenance of a constant level of vitamin A in the blood, possibly related to the activities of the reticuloendothelial cells. No such mechanism appears to exist for carotene. The occurrence of hypervitaminosis A in this child is interpreted either as indicating a defect existed in the system responsible for the protective reaction or else that intense, prolonged overdosage is capable of injuring the protective mechanism.

Johns Hopkins Hospital.

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CONCLUSION

On the basis of the results obtained in our metabolic studies we may conclude that while a congenital malformation of the primordial mesenchymal cell may exist we are certainly confronted by an associated metabolic disturbance which in its manifestations resembles a chronic state of hyperparathyroidism. Whether this disturbance is of maternal or fetal origin we cannot as yet definitely say.

Also previous observations concerning the chemical composition of marble bones have been confirmed in an uncomplicated case of this disease. The findings consist of hypermineralization, as indicated by a high ratio of inorganic to organic matter and an increase of the molecular ratio of calcium carbonate to calcium phosphate.

555 Prospect Place.

Case Reports

HYPERVITAMINOSIS A

JOHN A. TOOMEY, M.D., and RUSSELL A. MORISSETTE, M.D.
CLEVELAND

P. E., a 23 month old infant, was admitted to Babies' and Children's Hospital, Cleveland, on Dec. 22, 1944. The complaint was soreness and swollen legs.

Present Illness.—About Aug. 15, 1944, he fell. Soon afterward the right forearm became swollen and he complained of soreness along its radial aspect. On October 27, two days before admission to another hospital, a similar painful swelling began over the right shin which caused mobilization of the muscles of the right leg. He was irritable and anorexic. A tentative diagnosis of acute anterior poliomyelitis was made, but nothing was found to support it (*J. A. T.*). Roentgenograms of the bones showed them to be normal.

The child improved quickly, and within six days the pain and the tenderness disappeared, although a limp persisted. A possible diagnosis of acute periostitis was made. The patient received an indefinite amount of penicillin over a period of eight days.

Three weeks later (late in November) the signs and symptoms recurred, the involvement and the pain now being in both legs. He was readmitted to the same hospital on November 29 and was given penicillin therapy for six days, at the end of which time he was discharged. Repeated roentgenograms and blood counts revealed no abnormality.

One week later there was a second recurrence of pain and tenderness, this time in the forearms. In addition, he had anorexia, constipation and pruritus, and he was restless and irritable.

Past History.—The child had been breast fed, with supplemental formula feedings. Just before admission to Babies' and Children's Hospital he got meat, cereals and whole milk daily but no eggs or vegetables. The first twelve months of life he had no vitamin C, but had sufficient ascorbic acid since that time. He [illegible] from 1 to 2 teaspoons (from about 4 to 8 cc.) of cod liver oil daily from the age of 2 weeks. He stood at 7 and walked at 9 months.

Physical Examination.—The patient was normally well developed [illegible] acutely ill. His temperature was 37 C. (98.6 F.), his height [illegible] weight 11,175 Gm. The anterior fontanelle measured 0.5 cm. [illegible] of the face was erythematous, and there was roughening of the [illegible] the right leg; the lips were dry and cracked, and there was bleeding [illegible] of the mouth. The hair was coarse, dry and sparse. There [illegible] a few numbler, discrete, movable shot-sized lymph nodes in the anterior cervical and supraclavicular spaces. The chest was 46 cm. in circumference at the nipple line. The heart and the lungs were within normal limits. The abdomen was 49 cm. in circumference at the level of the umbilicus. The liver was palpable, its edges

Read before the Section on Pediatrics at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 3, 1946.

From the Jack & Heintz Laboratory, Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

smooth and about 2 cm. below the right costal margin. There was no splenomegaly. Considerable tenderness was elicited when the femurs were palpated.

The blood and urine were normal, and reactions to tests done with old tuberculin down to a dilution of 1 to 100 were negative, as were reactions of blood serums on two occasions.

A determination of erythrocyte sedimentation rate (Westergren) showed a fall of 14 mm. the first hour and 35 the second.

Chemical determinations are listed in the table.

Laboratory Data for Patient with Hypervitaminosis A

Date	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Mg./100 Cc.	Serum Proteins,* Mg./100 Cc.	Icteric Index	Nonprotein Nitrogen,† Mg./100 Cc.	Chole-sterol, Mg./100 Cc.	Lecithin, Mg./100 Cc.	Total Lipids, Mg./100 Cc.	Vitamin A: U.S.P. Units	Vitamin A: Micrograms‡	Carotene, Mg./100 Cc.	Vitamin C, Mg./100 Cc.
12/20/44	10.0	7.5	6.35	7.80	5								
1/ 6/45	10.4	4.5	6.35	6.0	5	..	....	....	....	280	67—	0	1.5
2/ 1/45	12.3	4.3	6.35	6.4	7	..	285	....	720	700	168—	Trace	0.9
2/20/45	....	....	....	....	..	31							
2/26/45	....	....	....	....	..	..	123	207	700	580	139—	Slight trace	1.0
3/ 5/45	11.6	4.3	6.35	....	..	..	180	210	522	540	127—	Trace	1.0
3/24/45	10.0	4.6	6.70	....	..	..	140	241	654	440	134—	0	0.5
4/13/45	12.2	3.4	6.60	4.8	..	..	185	223	543	1,300	310	0	
4/27/45	....	....	....	....	..	..	....	....	....	600	134—	0	
5/20/45	10.2	3.3	6.45	6.7	6	30	221	....	585	80	17—	0	

*Serum albumin, 4.1; globulin, 2.6; albumin-globulin ratio, 2:1 (normal 1.7:1 to 2:1).
†Creatinine, 1.1 (normal 1.2). Reactions to direct and indirect van den Bergh tests were negative.
‡The U. S. P. units were translated by Josephs into micrograms, 1 microgram equaling 3 units.

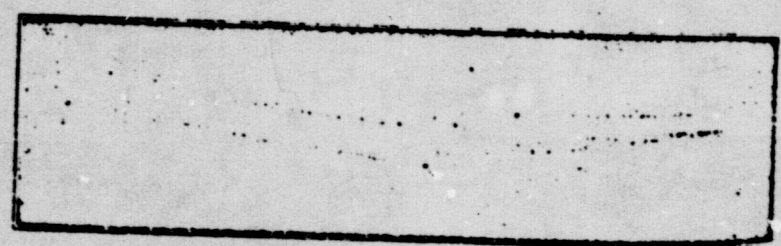

Fig. 1.—Roentgenogram showing condition in radius and ulna. Other roentgenograms of long bones were similar.

Roentgenograms of sinuses, the chest, etc., revealed no abnormality save for bilateral short cervical ribs. Those of the long bones revealed: (1) broad growth lines at the ends of all the long bones, (2) stippling of the distal femoral epiphyses, (3) fragmentation of the distal fibular epiphyses, (4) a periosteal line along the lateral aspects of the right femur and left tibia and (5) pronounced periosteal thickening on the posterior and the medial aspect of the ulnar bones. Stereoscopic roentgenograms of the skull were normal except for what appeared to be a minute foreign body in the scalp.

The course at the hospital was uneventful. After the first week he began to eat well, and a definite loss of weight was regained prior to his discharge. There was no diarrhea or vomiting; in fact, there were periods of constipation. The duration of the tenderness of the bones was about eight days. The skin remained essentially the same as described on admission.

He was discharged on the nineteenth hospital day with a diagnosis of probable healed or healing scurvy, and a high intake of ascorbic acid was recommended.

SECOND ADMISSION TO BABIES' AND CHILDREN'S HOSPITAL

On Jan. 31, 1945, three weeks later, he was readmitted. He remained in the hospital until April 23. The same symptoms were present, i. e., pain, swelling of the arms and legs and anorexia. At home and shortly after his previous discharge he had acute rhinitis, bilateral otitis media, swelling of the left eyelids and cervical adenopathy. On January 17 he contracted chickenpox followed by hematuria, which lasted about four days. Immediately before his admission, a red, dry rash had appeared around the neck folds. The diet during this period between hospital admissions had been limited almost exclusively to small amounts of milk, orange juice, preparations of vitamin D and various medications.

On examination, the lips were dry and fissured; there was peeling of the skin over the hands and feet, and there was left cervical lymphadenopathy.

Two days after his admission there was swelling of the skin in the neck folds and the skin of both shins. The child said that he felt "as if he had stones" in his shoes which made him walk on his heels. The stools were dark and tarry and contained fresh blood. About four days after admission he became more irritable than usual, was thirsty and drank a great deal and passed colorless stools. His mother thought that he favored his left leg and that he limped on that side.

She was cross examined about the boy's diet. He was the first and only child and of great concern to a conscientious mother. He was a "fussy eater," consuming no fruits and few vegetables. His customary daily diet consisted of some cereal, about 1 pint (473 cc.) of milk, 6 ounces (177 cc.) of orange juice, two tablets (25 mg. each) of ascorbic acid and 2 teaspoonfuls (8 cc.) of cod liver oil.

The patient appeared to be acutely but not severely ill. The temperature was 37 C. He weighed 11.8 Kg. The abnormalities noted were as follows: (1) healed varicella lesions; (2) mucopurulent crusts in the nares; (3) fissured and crusted lips which bled easily; (4) palpable nontender lymph nodes in the inguinal, axillary and left cervical regions; (5) a palpable nontender liver extending 2 cm. below the right costal margin and enlarged to the left nipple line; (6) an equisitely tender area (0.5 cm.) of swelling over the lower third of each radius, and (7) similar tumors over the lower third of each radius and over the lower third of both tibias, more obvious on the left. The swellings were not hot, shiny, erythematous or fluctuating and were in the bone structure rather than in the skin or the subcutaneous tissue.

The hemoglobin concentration was 85 per cent, the erythrocyte count 3,700,000 and the leukocyte count 15,400, with 41 per cent polymorphonuclear cells, 55 per cent lymphocytes and 4 per cent monocytes. The urine was normal. A leukocyte count of 23,800 was recorded on February 5, with the same proportions of the various types of cells as before. Platelet counts were 405,000 and 410,000 on two occasions, the bleeding time four and one-half minutes, the clotting time three to four minutes and the prothrombin time thirty seconds (control, twenty-nine

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seconds). Serologic reactions of the patient and the mother were negative. Erythrocyte sedimentation showed a fall of 40 mm. the first hour. The chemical analyses of the blood are noted in the table.

The vitamin A level was 240 micrograms per hundred cubic centimeters. The method used to determine this was referred to by Josephs [1] as the method of Clausen and McCord and was described by him in detail. Josephs stated that roughly 50 to 60 U. S. P. units per hundred cubic centimeters may be taken as a level dividing normal from abnormally low.

His mother was requestioned about the vitamins she gave her son, and this time she admitted giving the following: (1) a preparation of vitamin B complex, 2 teaspoons daily; (2) 1 dicalcium phosphate capsule daily; (3) grains (325 mg.) of saccharated ferrous carbonate twice daily; (4) 50 mg. ascorbic acid daily, and (5) percomorph liver oil with viosterol (Mead),[2] 1 teaspoon daily from the newborn period until October 1944 and then 2 teaspoons daily until the time of admission. His symptoms began shortly after the vitamins had been increased. The last preparation noted had not been given during each hospital stay, and each time he got better. It was learned that the patient was abnormally fond of butter, which he would eat by the teaspoonful.

About eight days after admission the periosteal pain and the tenderness disappeared, although the swelling and the dry, scaly condition of the skin remained for three weeks.

First Clinical Experiment.—Domagk and von Dobeneck,[3] as well as Willstaedt [4] and others, describe a symptom complex in rats produced by feeding moderately large amounts of vitamin A concentrate. The hair falls out, the eyelids are sealed, exophthalmos appears, the liver is large and there are spontaneous fractures of the bones.

No similar changes were found when large doses of carotene were ingested by guinea pigs,[5] rats[6] and rabbits.[7] Josephs [8] has published a report of a case

1. Josephs, H. W.: Studies in Vitamin A: Relation of Vitamin A and Carotene to Serum Lipids, Bull. Johns Hopkins Hosp. 65:112, 1939.

2. One teaspoon would equal approximately 250,000 units of vitamin A and 35,000 units of vitamin D. The information on the bottle is summarized as follows: "oleum percomorphum with other fish liver oils and viosterol, a liquid standardized to contain not less than 60,000 units of vitamin A and 8,500 units of vitamin D, U. S. P., per gram; approximately 1,250 vitamin A units and 180 vitamin D units per drop; source of vitamins A and D in which not more than 50 per cent of D is derived from viosterol."

3. Domagk, G., and von Dobeneck, P.: Ueber histologische Befunde bei der Ueberdosierung mit vitamin A-Konzentrat, Virchows Arch. f. path. Anat. 290: 385, 1933.

4. Willstaedt, H.: Die Vitamine: Jetziger Stand ihrer Chemie und Biochemie, Klin. Wchnschr. 14:841 and 1089, 1935.

5. Wells, H. G., and Hedenburg, O. F.: The Toxicity of Carotene, J. Biol. Chem. 27:213, 1916.

6. Davies, A. W., and Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A in the Organs of the Normal and Hypervitaminotic Rats, Nutrition Abstr. & Rev. 4:43, 1934.

7. Landy, M.: The Non-Toxicity of Large Amounts of Carotene, Department of Bacteriology, Ohio State University, unpublished data, 1934.

8. Josephs, H. W.: Hypervitaminosis A and Carotenemia, Am. J. Dis. Child. 67:33 (Jan.) 1944.

with an excellent discussion on hypervitaminosis A and carotenemia, and a complete bibliography is included.

With his mother's permission, an experiment to reproduce the clinical symptoms was started on the twenty-seventh hospital day. The level of vitamin A in the blood had by this time fallen to 500 U. S. P. units, or about 170 micrograms, per hundred cubic centimeters. He was given the same therapy as at home. This therapy was discontinued after eight days, for by that time the patient had become increasingly irritable and his skin was oily, scaly, rough and pruritic. He had been given approximately 4,000,000 U. S. P. units of vitamin A and 560,000 units of D. There was an obvious soft swelling over the distal ulna, which was painful and exquisitely tender. The level of vitamin A in the blood was greater than 800 U. S. P. units, or about 267 micrograms, per hundred cubic centimeters. The total fats were increased.

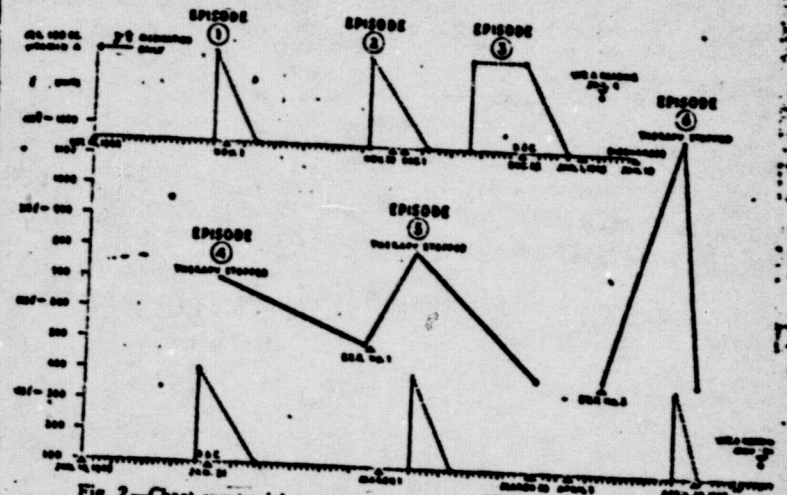

Fig. 2.—Chart summarizing case of hypervitaminosis A. The single solid line indicates the episode of pain, the dotted line the length of time the pain lasted and the double line the level of vitamin A in the blood.

As before, the symptoms and signs again disappeared about seven days after the vitamin therapy had been discontinued. The vitamin A level also fell at the same time and on March 26 was 400 units, or about 134 micrograms, per hundred cubic centimeters.

Second Clinical Experiment.—Was the condition of this patient caused by too much vitamin D? In this experiment he had received nearly 4,000,000 units of vitamin A, but he had also received over 500,000 units of vitamin D.

Again, with permission of the mother, an attempt was made to reproduce the syndrome, this time with a preparation which did not contain vitamin D.[9] One

9. A letter from E. R. Squibb & Sons contained the following information: "Vitamin A in oil is supplied in 1 cc. ampules, 100,000 units in each cubic centi-

(Footnote continued on next page)

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hundred thousand units was given daily for the first four days and then the dosage was increased to 600,000 units daily. On April 19 tenderness appeared over the radiuses and tibias. The vitamin A level was greater than 1,200 units, or about 400 micrograms, per hundred cubic centimeters and, to my knowledge, the highest ever recorded. Administration of the vitamin A preparation was discontinued after fourteen days, a total of 6,200,000 U. S. P. units of vitamin A and less than 640 units of vitamin D having been given by this time. The total fats were again increased.

On April 23, the day of discharge, the vitamin A level was 400 units, or about 134 micrograms, per hundred cubic centimeters, and clinical signs and symptoms had practically disappeared except for a persistent hepatomegaly.

The roentgenologic observations were the same as previously, although the lines noted on prior admissions in the right femur and the left tibia could not be visualized. There was a periosteal thickening of the middle third of both ulnas. Bone age was neither advanced nor retarded.

THIRD ADMISSION TO BABIES' AND CHILDREN'S HOSPITAL

He was hospitalized the third time on May 20, 1946, for the purpose of a check-up examination. At this time he had acute rhinitis, but otherwise appeared normal. Neither the liver nor the spleen was palpable. The hair was luxuriant; the areas of previous cutaneous lesions had healed. There were a few infected papules on the dorsal areas of the left and the right wrist. The chemical composition of the blood was normal, and the roentgenograms of the long bones showed only those changes incident to growth. There was no evidence of hepatic damage. The vitamin A level was less than 0.5 U. S. P. unit per cubic centimeter.

COMMENT

To my knowledge, no toxic effects have ever been described following the ingestion of carotene. Josephs[6] stated that carotene is less well absorbed than vitamin A and that the interval taken for this conversion prevents flooding the body with active vitamins, which is necessary for the toxic effects. The highest value of vitamin A in over 700 cases in which tests were made by Josephs did not exceed 250 U. S. P. units, or about 83 micrograms, per hundred cubic centimeters. At one time the patient he described had 910 U. S. P. units, or about 304 micrograms, per hundred cubic centimeters. My case presented the highest figures which I have found on record—over 1,200 units, or about 400 micrograms, per hundred cubic centimeters. Subsequent experiments at home with large doses of carotene were not controlled enough to be reported, but there were no symptoms other than a definite carotenemia.

Was this patient's condition due to vitamin A or a combination of vitamins A and D, or was he conditioned by vitamin D to vitamin A or vice versa? The clinical picture as described by Josephs was reproduced in my patient by the combination of vitamins A and D, but the same symptoms and signs were also reproduced by vitamin A without vitamin D. The symptoms stopped sooner than one would expect if vitamin D were the offending factor; still one cannot be absolutely certain that vitamin D did not produce some additive effect.

Josephs stated that there is no "safeguard" against the zeal of a layman who is persuaded of the value of vitamins, but that the zone of safety between the prophylactic and the dangerous dose of vitamin A is so large that many cases may not be expected, but that cases doubtless will occur. It took six months before the vitamin A content of the serum in his patient was within the upper limit of normal. The phosphatase content of the blood was still elevated two and one-half years later; the liver was still palpable with firm, sharp edges 2 cm. below the costal margin; the spleen was a large firm mass and the fingers were slightly clubbed; the skeletal development was slightly in advance of chronologic age (7 carpal centers of ossification at 5½ years). My patient was completely well on May 5, 1946 (about twenty months after his first illness), and had no evidence of hepatic damage. A distinctive feature of this case was the rapidity with which pain was produced and the equal rapidity with which it disappeared.

SUMMARY

A case of hypervitaminosis A is reported the features of which agree with the observations set down by Josephs: (1) hepatomegaly (but no splenomegaly), (2) increased levels of vitamin A in the serum, (3) increased level of serum lipids, (4) abnormalities of bones, (5) increased level of serum phosphatase, (6) low level of serum proteins, (7) sparse, coarse hair, (8) avid appetite for butter, (9) abnormal intake of vitamin A and (10) prompt recovery after exclusion of vitamin A from the diet. To these we should be able to add (11) pain and localized periosteal swellings and (12) recovery from pain when the vitamin A was withheld.

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DISCUSSION

Dr. Edward B. Shaw, San Francisco: I am not so much amazed by the fact that mothers occasionally give enormous dosage of such substances containing vitamins as percomorph liver oil as by the fact that infants usually withstand this overdosage without symptoms. One of my friends in nursing used to say, "It all shows what the human body will stand." There are so many vitamin preparations with a multiplicity of names and with different dosages as to leave the mother with some confusion regarding the dose to be administered.

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by Smyth. One member of this series is a patient whom I followed from the age of 6 months until the present, when he is about 3 years old. This child was presented with symptoms of discomfort resembling severe colic, and within the next little while soreness in his extremities developed which was thought to be due to scorbutic changes, although he was receiving some ascorbic acid. During the next few weeks, on adequate intake of ascorbic acid, swelling of both forearms and of both femurs and swelling about the mandible on both sides developed. There was no overlying redness, but the tenderness to pressure was even more pronounced than the swelling and there was striking resemblance to scurvy. This patient had an irregular low grade fever and a slight anemia but lacked the cutaneous changes, hepatomegaly and splenomegaly described by Dr. Toomey. Vitamin C levels in the blood were repeatedly normal and, most regrettably, the vitamin A levels were never determined. This child went on to slow improvement, which seemed to be accelerated by parenteral large doses of ascorbic acid, and he received generous, although never excessive, amounts of vitamins A and B. This case was one of a series presented by Smyth. A similar series has been presented from New York, in which utilization of ascorbic acid was thought to be the critical causal factor. There is enough resemblance between these patients to suggest a similar underlying cause. A further possibility, from which one could take off into the stratosphere of pure surmise, is that these symptoms might be provoked on one hand by faulty utilization of ascorbic acid and on the other by excessive amounts of vitamin A.

Dr. Joux A. Toomey, Cleveland: The question is whether this child's condition was due to vitamin A, to vitamin D or to a combination of both vitamins A and D. I cannot state definitely whether there was some effect due to vitamin D. The patient experienced symptoms when he was given vitamin A plus vitamin D, but when he was given vitamin A only, he also had symptoms. The patient became better and improved when the vitamin A was excluded. In the last experiment he was given only a small amount of vitamin D, 640 micrograms, a negligible amount. Recovery from overfeeding of vitamin D is never so quick as was the recovery of this patient when vitamin A was withheld.

The patient had symptoms when given vitamin A again and got better when it was withheld, only to have the symptoms recur when it was fed again.

He had no disturbance of vitamin C at any time or subsequently. The symptoms of scurvy are recovered from quickly as in this condition, but when swelling of the periosteum is present due to scurvy, absorption takes longer than it did in this condition.

Our patient received no other vitamins while the experiment was in progress save ascorbic acid and the vitamin D in the preparation. I feel that in this particular instance there was no damage done to this child. I have never found any reference in the literature mentioning any reaction to carotene.

AGENESIS OF THE LUNG

With a Review of the Literature

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LITTLE ROCK, ARK.

AGENESIS of the lung is a rare condition as shown by a careful review of the literature. A certain amount of confusion has arisen, however from the loose usage of the terms "agenesis" and "aplasia." "Agenesis" has been used for conditions ranging from complete absence of the lung and main bronchus to those in which a variable amount of pulmonary tissue accompanies a rudimentary bronchus. It would be advisable to conform to the more precise usage of the terms and to use "agenesis" for a failure of development and "aplasia" for incomplete development. Schneider [1] has classified congenital defects of this kind into three main types: (1) true agenesis with no trace of the lung, bronchus or vascular supply on the affected side; (2) a type characterized by small outpocketing from the trachea with a rudimentary bronchus but no pulmonary tissue present, and (3) a type in which a fully formed bronchus is present but which ends in a fleshy mass of areolar tissue of varying amounts. This classification has been generally accepted.

Hurwitz and Stephens [2] in 1937 found 34 cases reported in the literature, and in 1944 DeWeese and Howard [3] added 9 other cases. An additional 11 cases have been found in the literature and are listed in the table. This gives a total of 54 cases, to which is added 1 case. Since the advent of bronchoscopy an increasing number of cases have been reported in living patients (Garber,[4] Ferguson and Neuhauser,[5] Stokes and Brown [6] and Widerman and Peters.[7]) Other cases were

From the Department of Pathology, University of Arkansas School of Medicine Research Paper 834, Journal Series.

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2. Hurwitz, S., and Stephens, H. B.: Agenesis of the Lung: A Review of the Literature and Report of a Case, Am. J. M. Sc. 193:81, 1937.

3. DeWeese, E. R., and Howard, J. C.: Congenital Absence of a Lung Diagnosed Before Death, Radiology 42:389, 1944.

4. Garber, R. L.: Congenital Aplasia of the Lung, Am. J. Roentgenol. 53: 129, 1945.

5. Ferguson, C. F., and Neuhauser, E. B. D.: Congenital Absence of the Lung (Agenesis) and Other Anomalies of the Tracheobronchial Tree, Am. J. Roentgenol. 52:459, 1944.

(Footnotes continued on next page)

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Pediatrics 5:672-88 Apr. 1950

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CHRONIC POISONING DUE TO EXCESS OF VITAMIN A

Description of the Clinical and Roentgen Manifestations in Seven Infants and Young Children

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DURING 1945 the author observed a girl 25 months of age who had cortical hyperostoses in many sites of the skeleton. Her disease began when she was 19 months of age. She was described as a probable example of infantile cortical hyperostosis,[1] although at that time there was some question of the validity of including, in the syndrome of infantile cortical hyperostosis, patients such as this one who exhibited neither facial swellings nor mandibular hyperostoses and in whom the onset appeared after the first four months of life. Later it was learned that this patient had been taking one teaspoonful of oleum percomorphum daily for "several months" before the symptoms appeared. The author now has records of seven patients who ingested excessive amounts of vitamin concentrate A and D over long periods and who present similar clinical, roentgenographic and chemical findings. The subject of this report is a description of the toxic signs and symptoms in this group. The morbid anatomy of the lesions is unknown; there have been no biopsies or necropsies.

CASE REPORTS

Case 1. A. M., a girl 25 mo. of age, had complained of anorexia for 6 mo. and pain in the legs for 4 mo. She had been well until the 19th mo. when she became fussy, tired easily and began to refuse most of the food offered. During the 21st mo. the left shank and foot became swollen and painful; she refused to walk and the left shoe could not be worn because the foot was too large and tender. On several occasions she had heavy sweats at night.

Physical examination disclosed malnutrition, dry cracked lips, bilateral palpable clavicular swellings, and a tender firm swelling in front of the left tibia. These swellings were all deep, firm, not overly warm, not discolored and unattached to the skin. There was a similar swelling in the left foot. She refused to stand or to walk. Liver was not enlarged to palpation. She was and remained afebrile.

Hemogram and urinary examinations were normal. Blood proteins were present in normal concentrations (albumin 4.6 gm., globulin 2.3 gm./100 cc.), as were the serum calcium and phosphorus (10.6 mg. and 4.3 mg./100 cc., respectively). Blood NPN was 34 mg./100 cc. Serum phosphatase activity equaled 18 Bodansky units. ESR was 22 mm. in 1 hr. (Westergren). Blood serum gave a nonsyphilitic reaction to Kline's test. No serum agglutinins for the typhoid-dysentery-cholera group of bacteria were found in dilutions of 1:20 or higher.

Roentgen examination of the skeleton revealed cortical hyperostoses in both clavicles, in the right and left 7th ribs, both ulnas, right femur, left tibia, right fibula, and in all of the metatarsals in both feet, save the 1st metatarsals (Fig. 1). The mandible and the cranium were normal roentgenographically. There were no destructive changes anywhere in the skeleton and the bones unaffected by hyperostosis were all normal. Maturation of the skeleton was normal.

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The course in the hospital was striking. At first all food was refused and the patient was inactive, apparently from painful pseudoparalysis associated with the tender swellings in the legs and feet. After a few days she was feeding herself and taking a normal diet in normal amounts. At the end of about 4 days, most of the pain and tenderness had subsided although the swellings persisted. A bone biopsy had been planned but this was cancelled owing to the rapidity of recovery.

During the 2nd wk. of hospital residence it was learned from the mother that she had voluntarily increased the dose of oleum percomorphum* several months before so that the child had been receiving daily approximately 150,000 u. vitamin A and 22,000 u. vitamin D. This dosage had been stopped on admission to the hospital and clinical improvement was almost immediate.

After 22 days of hospital residence the patient was discharged asymptomatic. In roentgen films made 3 mo. following discharge, the hyperostoses were still visible but were all smaller and more sclerotic than before. One year later the hyperostoses were invisible roentgenographically. She has had no recurrence of symptoms for 4 yr.

Case 2. B. K., a girl, was 21 mo. of age when she was first seen in consultation with her pediatrician who had made a diagnosis of infantile cortical hyperostosis. She had been well until the 19th mo. when she became restless and "whiny" and a painful tender lump appeared on her right shin. For 3 wk. she had been refusing food and was unwilling to walk. Penicillin intramuscularly did not modify these manifestations. At the same time she became hyperirritable; insomnia was marked and she sweated excessively at night. She screamed when the weight of the bed clothes was on her, and resisted attempts to dress her, put on her shoes or change the diaper. Two weeks before, tender swellings first made their appearance in the left forearm and on the dorsum of the right foot. One week prior to the consultation a large hard lump appeared over the occiput but there were no facial or mandibular swellings. The temperature never exceeded 37.8°C.

In the physical examination the 21st mo., she was found to be exceedingly irritable and apprehensive of being touched. Photographs and roentgen films were made with great difficulty. The lips, especially the lower lip, were dry and cracked. Deep, firm, tender swellings were visible and palpable in the occipital region, in both forearms, on the ventral surface of the right shank, and in the lateral aspects of the dorsum of both feet (Fig. 2A and B). Liver was not enlarged and temperature was normal.

Hemogram and urinary findings were normal. ESR was 24 mm. after 1 hr. Multiple cortical hyperostoses were demonstrated by roentgenographic examination in both ulnas, left tibia and in both 5th metatarsals (Fig. 2C, D and E). Mandible was normal and there was no sign of bone production under the large swelling in the occipital region. The mother on being questioned in more detail about vitamin intake related that she had been giving the patient 1 teaspoonful of oleum percomorphum daily since the 12th mo. of life, which meant that this child had received 200,000 to 300,000 u. vitamin A daily over a period of about 9 mo. Blood withdrawn at this time showed a concentration of 330 u. of vitamin A/100 cc. plasma (normal 50-150); blood carotene was 70 gammas/100 cc. (normal 40-200 gammas).

Oleum percomorphum was stopped and within 4 days the patient was asymptomatic, although swellings were still present. She began to take normal amounts of food; the pain, tenderness and hyperirritability disappeared completely and sleep was undisturbed. The swellings gradually diminished in size so that they could not be detected after about 2 wk. In films, the hyperostoses in the 5th metatarsals were barely visible at the end of 6 wk. although, at the same time, the ulnar and tibial hyperostoses were only slightly diminished in size and much denser than earlier. At the end of 1 yr., all the hyperostoses were invisible save slight residual thickening in the cortical walls of the ulnas and the right tibia. The patient has thrived during the last 23 mo.

Case 3. H. A., a boy 12 mo. of age, was referred for roentgenographic examination with the clinical problem of soreness of the left shoulder and swelling and failure to use the left arm. These symptoms had been present for approximately 3 wk. The referring pediatrician suspected unrecognized traumatic injury to the left shoulder joint. There were no constitutional symptoms; the appetite had remained good and there had been no fever.

Roentgenographic examination disclosed ulnar hyperostoses (Fig. 3). Remainder of the skeleton,

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* Oleum percomorphum (Mead Johnson) is made up of liver oils of the percomorph fishes, sterol and other fish oils. It is standardized to contain not less than 60,000 u. vitamin A and 000 u. vitamin D/gm.

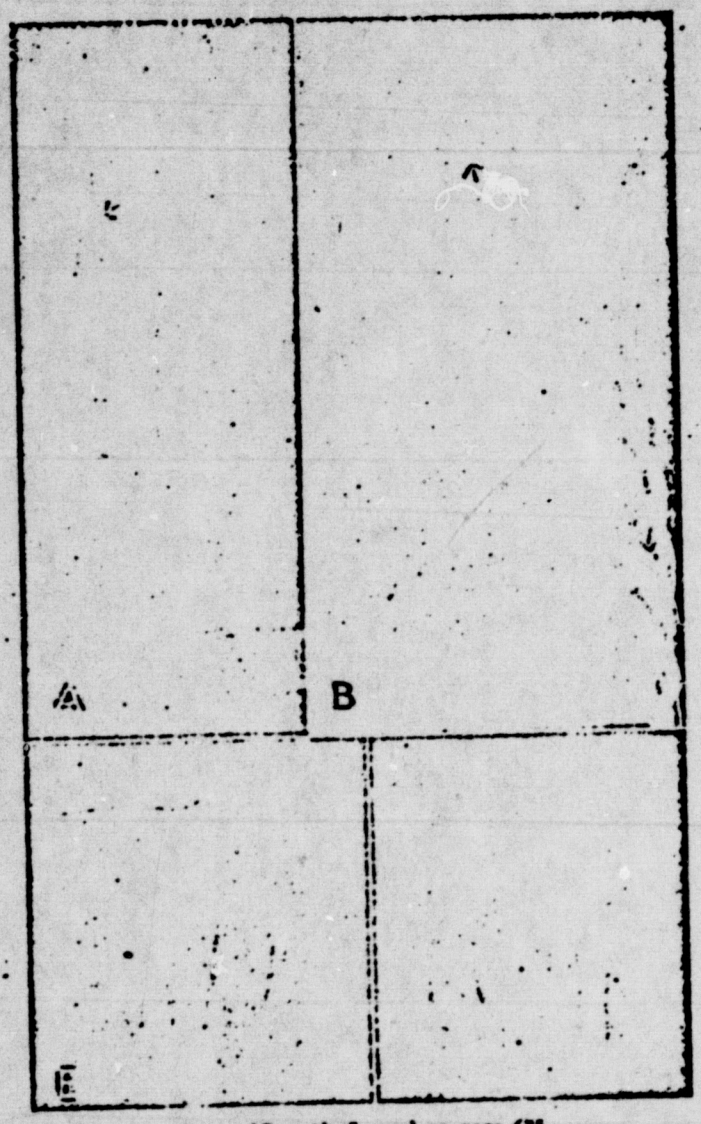

FIG. 1 (Case 1). Legend on page 675.

including the mandible and bones of the feet, were normal roentgenographically at this time. A presumptive roentgen diagnosis of hypervitaminosis A was made on the basis of the symmetric ulnar hyperostoses and, on direct questioning, the father stated that the infant had been receiving 2 teaspoonfuls of oleum percomorphum daily during the preceding 6 mo. (400,000 to 600,000 u. vitamin A/day). The family pediatrician later reported that the mistake in dosage was due to error in purchase at the drug store. The mother had supposed she was getting cod liver oil and the druggist was under the impression that she ordered oleum percomorphum.

Infant was well nourished, without pallor or fever. There were many large and small patches of erythema in the skin and in these areas numerous scratch marks were present. Pruritus had not been recognized by the parents. In the left forearm there was a long, poorly defined, firm tender swelling which was not discolored or overly warm. Liver was not enlarged.

Blood count and urinary findings were normal. ESR was 24 mm. after 1 hr. Serum calcium was 9.9

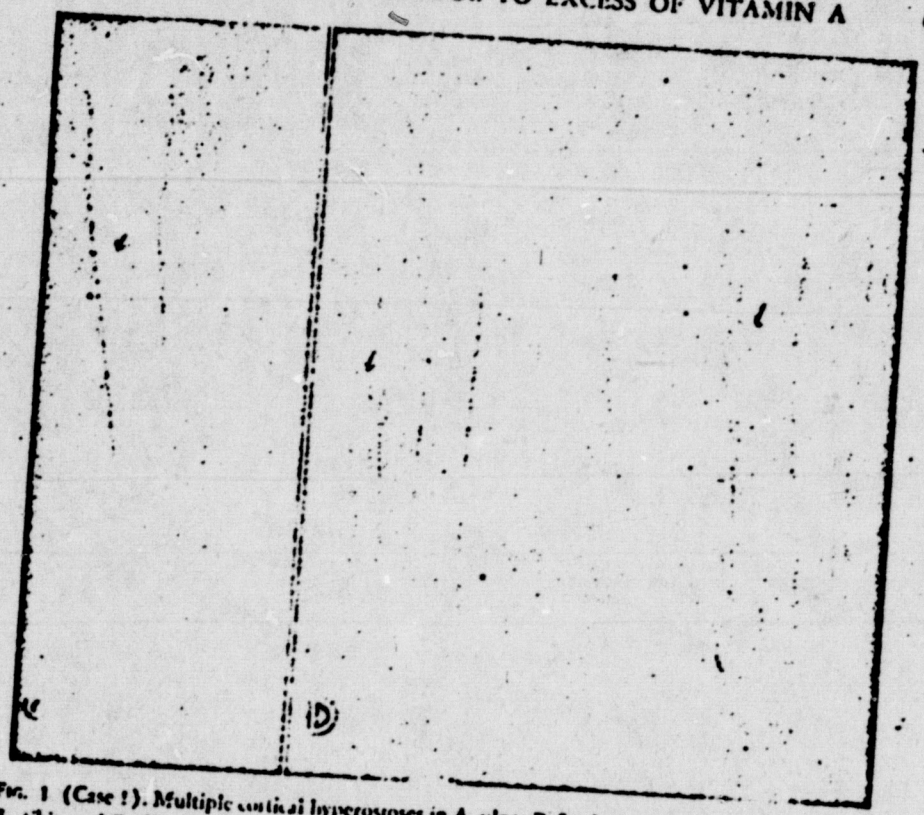

FIG. 1 (Case 1). Multiple cortical hyperostoses in A. ulna; B. L. clavicle and L. 7th rib; C. R. femur; D. L. tibia and R. fibula; E. 2nd, 3rd, 4th and 5th metatarsals in both feet. First metatarsals are not affected.

mg./100 cc.; phosphorus 4.8 mg./100 cc.; serum phosphatase activity equaled 15.2 Bodansky u. Kline's test on blood serum gave a nonsyphilitic reaction. Concentration of vitamin A in blood plasma was 1384 I.U./100 cc. (normal 50-150); total blood lipid was 840 mg./100 cc.; blood carotene concentration equaled 146 gammas/100 cc. (normal 40-200).

The ingestion of vitamin concentrate was stopped and pain and tenderness in the left arm disappeared after 4 days. The patient has remained asymptomatic. In films of the skeleton made 10 wk. later, the ulnar hyperostoses were still visible but were smaller and more sclerotic; in films of the feet, symmetric hyperostoses of the 2nd metatarsals were now visible although they had not been visible in the earlier films and the patient had never had signs or symptoms in the feet.

Case 4 (Dr. A. Ashley Weech, Children's Hospital, Cincinnati). W. K., a boy, was first seen at 32 mo. of age when he complained of painful feet of 3 wk. duration. Twelve days before, tender swellings appeared in the left hand, left arm and left shin. He became generally irritable but had no fever and retained a normal appetite. During the 10 days prior to admission, there had been several nosebleeds. On admission the parents stated that he had been receiving 2 teaspoonfuls of cod liver oil daily.

The boy was well nourished and mentally alert. Liver edge was at the costal margin. In the left forearm there was a long, hard, tender swelling over the ulna. The swelling was not overly warm or discolored. There were similar swellings on the left thumb, over the left 2nd metacarpal and over the left tibia. Regional lymph nodes were not enlarged. Both feet and one wrist were also slightly swollen. There was no reaction of the skin to tuberculin or histoplasmin.

Findings in the blood count and urine were normal. Kahn's test on the blood gave a nonsyphilitic reaction. Serum calcium was 10.7 mg./100 cc.; phosphorus 4.8 mg./100 cc.; serum phosphatase activity equaled 19 Bodansky u. Blood protein nitrogen was 30 mg./100 cc.

FIG. 2 (Case 2). Legend on page 677.

Roentgenographic examination of the skeleton disclosed hyperostoses in the 2nd left metacarpal (Fig. 4), both ulnas, both tibias and the fibula. In the feet both 4th metatarsals were thickened. The bones of the head and chest were normal roentgenographically and maturation of the skeleton was normal.

The course in hospital was uneventful. Before discharge it was learned that the mother had been giving the child oleum percomorphum instead of cod liver oil. Three years later the history was reviewed again with the mother. In review she stated that 10 drops of oleum percomorphum* were given daily from the 6th wk. until the 17th mo. of life. During the 17th mo., the child had a severe laryngotracheitis and the mother, deciding that more vitamins would be beneficial, increased the dose to 1 teaspoonful of oleum percomorphum daily. This dose had been continued during the 15 mo. which preceded admission to hospital.

Case 5 (Drs. S. Z. Levine and John Dale, Jr., New York Hospital, New York City). A. C., a boy 18½ mo. of age, was admitted with a chief complaint of pain in the bones of a few weeks' duration. Appetite had always been poor. Drisdol® with vitamin A,* a vitamin concentrate of A and D, had been started at 1 wk. of age when a "dropper-full" was given daily. After the 12th mo., the vitamin concentrate was increased to ½ and later ¾ teaspoonful daily, which provided about 125,000 u. vitamin A and 20,000 u. vitamin D. After the 13th mo., 1 teaspoonful of drisdol® with vitamin A. (about 250,000 u. vitamin A and 40,000 u. vitamin D) was given daily. Two weeks before admission he was said to have bruised his leg in a fall and had had pain in his legs.

Examination disclosed that he was hyperirritable and afebrile. Both hands were swollen and tender. Liver edge was 2 cm. below the right costal margin. Left shank and both forearms were swollen and tender.

Hemogram and urinary findings were normal. ESR was 27 mm. after 1 hr. Serum calcium was 10.5 mg./100 cc.; serum phosphorus 3.6 mg./100 cc.; serum phosphatase activity equaled 9.7 Bodansky u. Vitamin A concentration in the blood plasma was 1395 u./100 cc. (normal 80-200); blood carotene was 73 gammas (normal 30). Vitamin C content of the leucocytes was 4.2 mg./100 cc. (low). The Mazzini blood test gave a nonsyphilitic reaction.

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* Drisdol® with vitamin A is a solution in sesame oil of drisdol, vitamin D2 from ergosterol, and natural fish liver oils. Each gram contains 30,000 u. U.S.P. vitamin A and 10,000 u. vitamin D.

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. 2 (Case 2). Tender swellings and hyperostoses after 9 mo. of ingestion of excessive amounts
ms percomorphum(D). A. Ulnar swellings in forearms and fissuring of lips; B. symmetric swell-
ver 5th metatarsals and over R. tibia; C. long wavy cortical hyperostosis of ulna; D. symmetric
ings of cortices of 5th metatarsals; E. long wavy cortical hyperostosis of R. tibia; striking
e of metaphyseal and epiphyseal changes.

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FIG. 3 (Case 3). Bilateral ulnar hyperostoses, 3 wk. after onset of soreness in arms, and after 12 mo. of intake of 2 teaspoonfuls of oleum percomorphum daily. Remainder of skeleton was normal roentgenographically, including feet. However, 10 wk. later and 10 wk. after oleum percomorphum had been stopped, symmetric hyperostoses of 2nd metatarsals were demonstrated roentgenographically.

Roentgenographic examination of the skeleton disclosed cortical hyperostoses in both clavicles, 6th and 7th right ribs, both ulnas, right radius, left tibia, right fibula, 4th and 5th right metatarsals and both 4th metacarpals (Fig. 3). Mandible was normal, as was skeletal maturation.

In the hospital the daily vitamin intake was reduced to approximately 12,000 u. vitamin A, 1,800 u. of D and 30 mg. ascorbic acid. Clinical recovery was rapid. He became active and asymptomatic; after 6 wk., he had gained 0.9 kg. The plasma concentration of vitamin A fell to 700 I.U. on the 12th hospital day, 500 I.U. on the 20th hospital day, 400 I.U. on the 27th day and 360 I.U. on the 37th hospital day.

Case 6. R. B., a boy 24 mo. of age, complained of pain, tenderness and swellings of the extremities for about 2 mo. According to his mother, he had always been in good health prior to the present complaints and had been taking the "usual" amounts of vitamin concentrates. The first symptoms were pain and swellings in the forearms, especially on the right side. One month later his shanks and ankles became swollen. At this time roentgenographic examination had shown symmetric hyperostoses in the ulnas. The feet and ankles became so swollen and tender that he could not wear his shoes. Immediate roentgenographic examination then disclosed no abnormal changes in the bones of the feet

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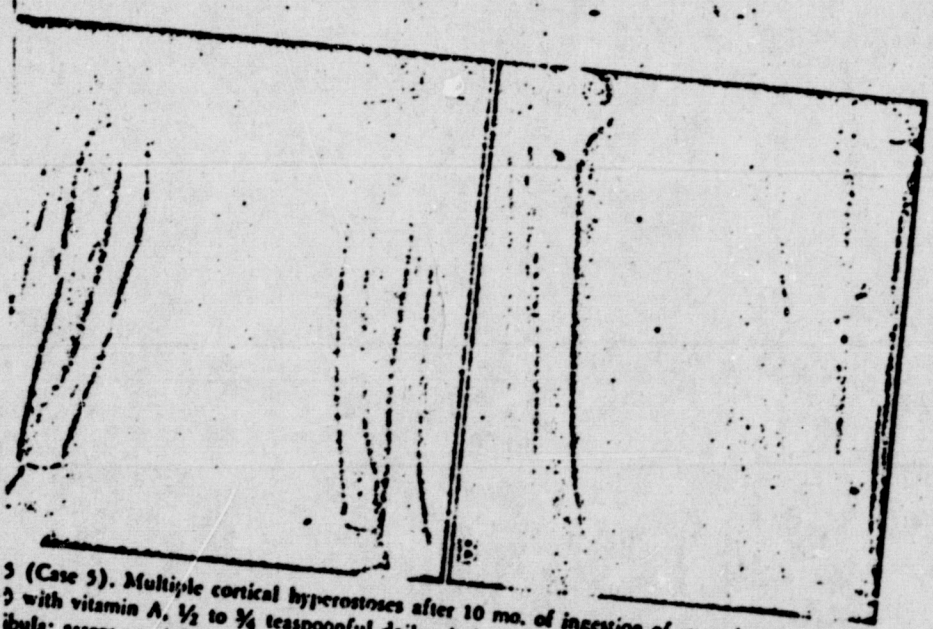
. 4 (Case 4). Cortical thickenings of 2nd metacarpal 3 wk. after appearance of tender swellings in hand. This patient had received 1 teaspoonful of oleum percomorphum daily for 15 mo.



5 (Case 5). Multiple cortical hyperostoses after 10 mo. of ingestion of excessive amounts of with vitamin A, ½ to ¾ teaspoonful daily: A. in both ulnas and one radius. B. in L. tibia ibula; arrow on right points to cortical defect not related to hypervitaminosis A.

or shanks. During the first weeks of the illness, fever occurred for short periods and then disappeared completely.

When examined by the author 2 mo. after onset, there were no abnormal physical signs. The swellings could not be identified clinically. In the roentgenographic examination, however, cortical thickenings were visible in both ulnas and in the 5th metatarsal (Fig. 6).

The family was requestioned 2 yr. later and it was then learned that the mother, who had given the original history, had had little to do with the care of the child during his 1st 2 yr. Actually he had lived with and been under the care of his grandmother. She stated that oleum percomorphum had been given daily since the first weeks of life, starting with a few drops daily with gradual increases to ½ teaspoon daily. During the 7 mo. prior to onset of symptoms, the boy received approximately 100,000 u. vitamin A every day.

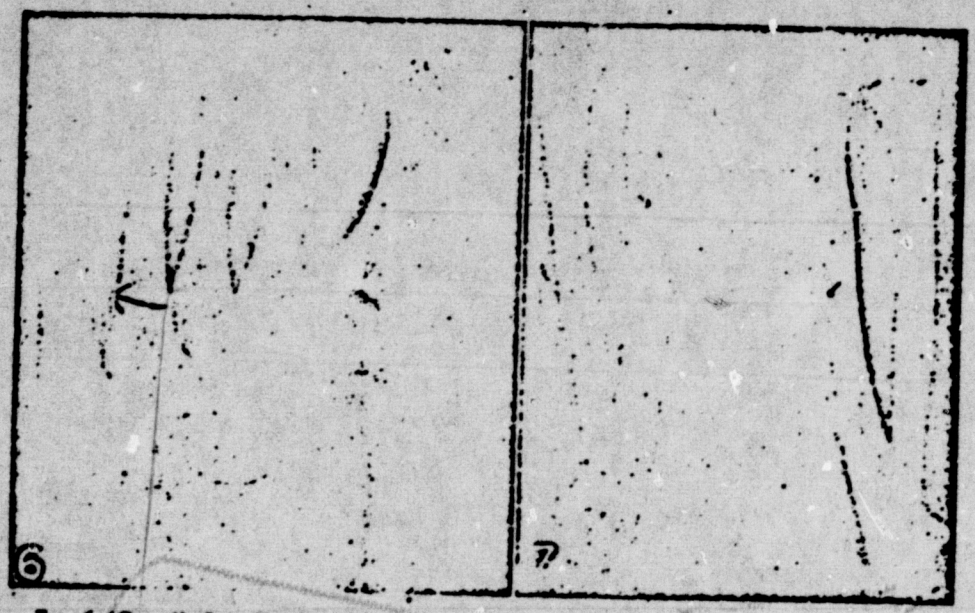


FIG. 6 (Case 6). Lamellated cortical hyperostosis of L. 5th metatarsal 9 mo. after beginning ingestion of ½ teaspoonful of oleum percomorphum daily. Two ulnas were only other bones affected.

FIG. 7 (Case 7). Symmetric, bilateral thin hyperostoses of ulnas after 15 mo. of ingestion of excessive amounts of navitol® in daily dosage of 1 teaspoonful, which provided approximately 200,000 u. vitamin A daily. Both clavicles were also thickened.

After a few days of hospital residence, the patient went to live with his mother and remained permanently asymptomatic.

Case 7 (Dr. Frederic N. Silverman, Children's Hospital, Cincinnati). R. B., a boy 37 mo. of age, had had a pruritic rash on his buttocks and back for 5 mo. His arms and legs had been tender for 2 mo. He frequently limped and refused to bend over owing to pain. He had been afebrile. His skin was dry and contained many scratch marks. The liver edge was 3 cm. below the right costal margin. He whined with pain when manual pressure was made on his legs and arms, especially when deep palpation was attempted. Blood count disclosed a mild anemia; there were 9 thousand leucocytes/cmm. with normal differential count. Serum calcium was 10.8 mg./100 cc.; serum phosphorus 5.2 mg./100 cc.; phosphatase activity of the serum equaled 22 Bodansky u. Roentgenographic examination of the skeleton disclosed cortical hyperostoses in both clavicles and both ulnas (Fig. 7). The bones of the feet were not filmed.

The cause of these clinical manifestations and roentgen changes remained unexplained until 4 yr. later when the mother was requestioned concerning the patient's intake of vitamin concentrates. The mother referred to the written records in her baby book and then stated for the first time that

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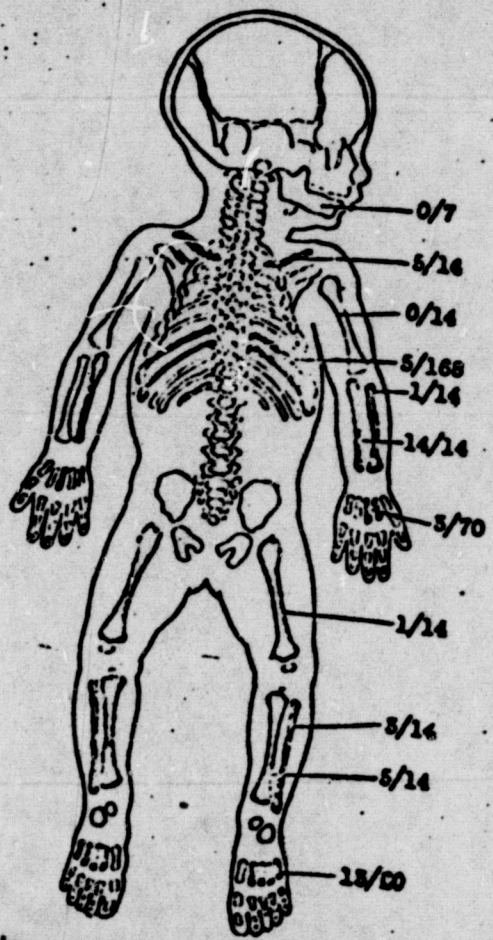
navitol®,* a concentrate of vitamins A and D, had been started on the 10th day of life and 10 drops daily had been given until the 20th mo. During the 20th mo., the child suffered from a respiratory infection and the mother increased the dosage of navitol® to 1 teaspoonful daily (200,000 to 300,000 u. daily vitamin A). This excessive intake had been continued for 17 mo. prior to admission to the hospital. The patient recovered quickly in the hospital and has remained well for the ensuing 4 yr.



. Distribution of hyperostoses in 7 patients. Shaded bones were hyperostotic and numbers each shaded bone indicate total number of such affected bones in all 7 patients on both sides In every patient both ulnas were thickened and in every patient some of metatarsals were First metatarsals, however, were not affected in any patient.

COMMENT

poisoning due to the ingestion of large single doses of vitamin A is rare but has occasionally when children have swallowed an entire (50 cc.) bottle of oleum phum.[2] Under these circumstances, the only clinical manifestations have been nausea and vomiting. The toxicity of polar bear liver to Arctic travellers, Eskimos,

liver concentrate containing 65,000 u. U.S.P. vitamin A and 13,000 u. U.S.P. vitamin

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and their dogs has long been recognized; apparently it is due to the high content of vitamin A. Poisoning from this source is said to be characterized by headache and hyperirritability during the first 24 hours, followed by an irresistible desire to sleep. Desquamation of the skin begins at the mucocutaneous junctions of the lips during the second 24 hours, with rapid spreading until the entire skin peels in a few days. Several parties of Arctic explorers have been poisoned in this fashion and a number of deaths have been reported. Rodahl[7] found the vitamin A content in polar bear liver approximated 18,000 u./gm. He estimated that the ingestion of 0.5 kg. of polar bear liver represented an intake of approximately 8,000,000 u. of vitamin A.

Moore[8] found a wide variety of toxic manifestations in experimental vitamin A poisoning in small animals. He observed roughening of the hair, alopecia, generalized seborrhea, enteritis, pneumonia, emaciation, softening and fractures of the long bones, and sudden profuse internal hemorrhage. Wolbach[6] and Maddoch, Wolbach and Maddoch[8] made comprehensive studies of the skeletal changes produced by excess vitamin A in small animals. They report that all features of skeletal maturation are accelerated: endochondral bone formation and subperiosteal appositional growth of the cortex. The rapid and excessive tubulation of rat bones resulted in tubular bones of smaller caliber than normal, in contrast to the swollen thickened shafts which have been observed in all the human examples of clinical vitamin A poisoning. Many of Wolbach's animals, especially the

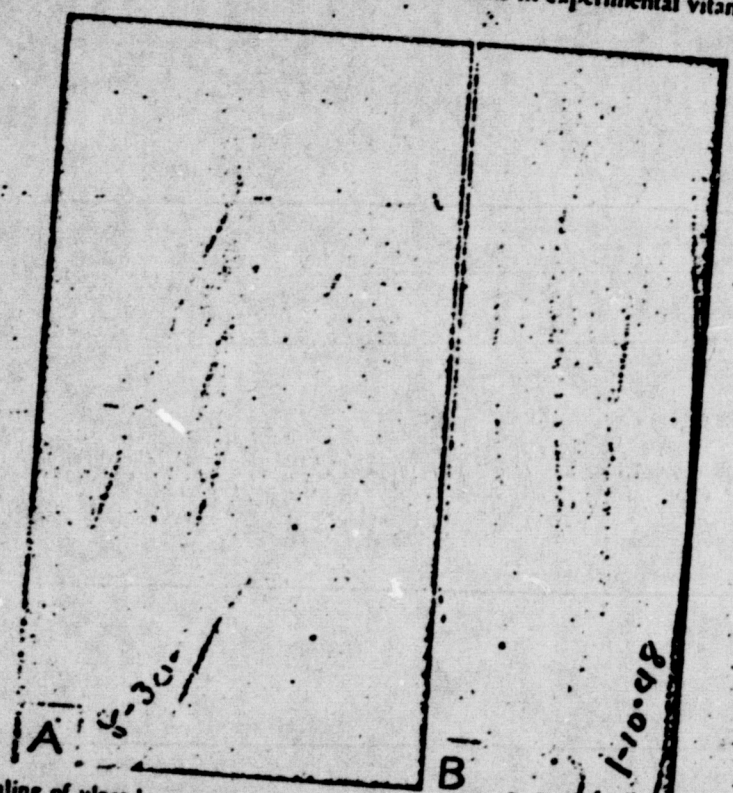

FIG. 9. Healing of ulnar hyperostosis in Case 2. A. Thin, wavy, shell-like cortical thickening during active phase of poisoning at admission. B. Four months after stoppage of vitamin concentrate; same hyperostosis is shrunken, smooth and more sclerotic.

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younger growing ones, developed fractures after 6 to 10 days of high intake of vitamin A.

There are five examples of chronic vitamin A poisoning in infants and younger children reported in the literature. Josephs[6] first pointed out the dangers of high vitamin A intake in pediatric prophylactic practice and first demonstrated the value of the increased blood content of vitamin A in diagnosis of its poisoning. He described hypervitaminosis A in a boy 34 months of age who had received one teaspoonful of halibut liver oil (2,000 I.U. vitamin A) daily after the third month of life and occasionally drank the oil directly from the bottle. Toomey and Morrisette[7] first observed deep, hard, tender swellings in the extremities and were the first to describe cortical thickenings in tubular bones. Their patient was a boy 23 months of age who received one teaspoonful of oleum percomorphum daily from the second week until the 19th month and two teaspoonfuls from the 19th month until the 23rd month. After stoppage of oleum percomorphum and subsidence of clinical signs, Toomey and Morrisette reinduced the clinical signs by refeeding oleum percomorphum, and then a second time by feeding pure vitamin A.

Dickey and Bradley[8] reported tender swellings and cortical hyperostoses in a child 22 months of age who was poisoned by navitol[10] fed in daily dosage of three teaspoonfuls. Two patients of Rothman and Leon,[9] who were poisoned by excessive dosage of oleum percomorphum, exhibited tender swellings, cortical hyperostoses and high blood content of vitamin A. In all recorded cases, with the exception of the case of Josephs, rapid recovery followed the stoppage of ingestion of vitamin concentrate containing vitamin A.

In the group of seven patients reported here, the principal toxic manifestations were similar to those previously described; the roentgenographic observations are more complete and more detailed than those in earlier reports. Data in 12 cases now provide the opportunity for a more complete presentation of the clinical picture and a better insight into the differential diagnosis. Current findings in a comparatively large number of patients also make possible a comparison of hypervitaminosis A and infantile cortical hyperostosis, a syndrome with which vitamin A poisoning has been confused. It seems certain now that the two older patients described in 1946 (Caffey,[1] cases 2 and 5) as examples of infantile cortical hyperostosis actually suffered from excess vitamin A.

In all these patients, the excessive intake of vitamin A was unknown to their pediatrician and was not recorded in the original hospital histories. In three cases the history of overdosage was not obtained until two, three and four years after discharge from the hospital. Customarily, in history-taking, the interest in vitamin intake is directed exclusively at insufficiency of intake and the question of excessive intake is not raised. If overdosage is to be detected early from the history, the actual frequency of feeding and amounts of vitamin concentrate fed, the method of measuring the amount and the preparation used must all be sought for in detail. Apparently it is not an uncommon practice for mothers to stop measuring vitamin concentrate accurately, drop by drop, soon after they start its use; to save time the estimated dosage is poured directly from the bottle into a teaspoon. Under these circumstances the error of estimate appears to be invariably in the direction of overdosage. In one of the cases, the mother stated that she had been giving 20 drops of oleum percomorphum daily but, on further questioning, recalled that she had not been measuring each dose; actually she had been feeding the contents of one bottle of 50 cc. of oleum percomorphum each month. The infant had received about 70 drops each day instead of the 20 drops daily originally stated. Knowledge of the frequency and the amount of vitamin concentrate purchased may be more informative than the mother's statement of the unmeasured daily dose. The physician must also make certain that informants, especially fathers and grandmothers, actually know the details

of vitamin feeding. The possibility of confusion between oleum percomorphum and cod liver oil at the time of purchase should also be borne in mind.

All these parents were wholly ignorant of the harmful effects in higher doses of the vitamin concentrates recommended to them in small doses for prophylaxis. The parental reasons for giving toxic doses are interesting and important. In one case, the mother simply decided that, if a small amount of the concentrate was good for the baby's bones, a larger amount would be better. One grandmother increased the dosage to make sure that she was doing a better job at prophylaxis than the mother had been doing. In two cases the reason for higher dosage was never satisfactorily explained; apparently these mothers, ignorant of potential dangers, increased dosage in the blind belief that plenty of vitamins would promote the health of their children. In two instances dosage was increased and then toxic doses were continued in the hope of combatting and preventing upper respiratory infections. In another case, not reported in this group, the mother stated that her infant had developed such a fondness for oleum percomorphum that she had to feed one teaspoonful daily to keep the baby satisfied. In another instance the mother was unwittingly feeding oleum percomorphum instead of cod liver oil.

The estimated daily intake for these patients varied from about 75,000 to about 500,000 u. vitamin A. The data in this regard are difficult to evaluate precisely. In some cases the actual dosage was underestimated by the mother. On the other hand, such factors as incomplete filling of the teaspoon, spillage during feeding and spitting out of some of the concentrate by the infant may well have lessened the actual intake and absorption in comparison with the amount fed, as stated in the history. It should be emphasized that in no case was overdosage due to erroneous advice by a physician or erroneous labelling of the bottle by the manufacturer. It is equally true, however, that in no case did a manufacturer's label state the harmful effects of overdosage nor had any mother been so advised by her pediatrician. This failure to point out clearly the dangers of excess feeding of vitamin concentrates is a serious error of omission and should be corrected.

There are several possible toxic elements in the concentrates of vitamins A and D in fish oils, which presumably might have been the toxic agents in these patients. Vitamin D is an unlikely toxic factor because it had been used clinically in considerably higher dosages without toxic effect; also when children have been poisoned by massive administration of vitamin D, they have not exhibited signs and symptoms like those in this group. According to Debré,[10] the toxic manifestations of vitamin D poisoning in children include anorexia, polydypsia, renal damage, increased blood urea and blood calcium, and extraskeletal calcifications. There are some toxic proteins in several types of fish liver, notably halibut liver; supposedly, even minute traces of the liver proteins are removed from fish liver oils in the current methods of their extraction and processing.[11] Toomey and Morrisette[9] performed the crucial clinical experiment of feeding excess of vitamin A to their patient and reproduced the clinical picture of hypervitaminosis A. These facts all indicate that the toxic component of the vitamin concentrate fed to our patients was vitamin A.

There are several characteristic features in the clinical picture. In all cases there was a long latent period of several months between the start of excessive dosage and the appearance of diagnostic clinical signs. The length of this latent period did not depend on the size of the overdose. The shortest latent period was six months; the longest was 15 months. The appearance of tender swellings has been used as the criterion for the

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set of the clinical disease. In some cases pruritus and anorexia preceded tender swellings several weeks or months; anorexia and pruritus are so common in children who do t suffer from hypervitaminosis A that their significance in children poisoned by vita- n A is exceedingly difficult to evaluate from a causal standpoint. Since anorexia is a ominent feature of vitamin D poisoning, it is possible that vitamin D played a part the causation of anorexia in these patients. In Case 3, however, appetite remained rmal during a period of six months of excessive vitamin concentrate feeding and for ee weeks after the appearance of tender swellings. Enlargement of the liver has been nd by others in several patients; the liver was normal in size in all the patients ex- ined personally.

Tender swellings, hyperirritability and limitation of motion all became evident at ut the same time. Tender swellings were most common in the forearms but they were e conspicuous in the shanks and feet in some patients. Swellings were always deep and ly attached to underlying structures, apparently the bones. The overlying skin in con- was always freely movable over the deeper masses and was never edematous or dis- red. Tenderness appeared to be moderate and local heat was not increased. All types andling were feared and resisted. Large temporal and occipital swellings developed vo patients but the mandible and face were always normal in all patients. Lymph s, regional to the swellings, were not enlarged.

perostoses in two or more of the long bones were identified roentgenographically ery patient; the distribution and frequency of involvement of different bones are n in Figure 8. Hyperostoses were found under all of the soft tissue swellings which be demonstrated clinically. All the 14 ulnas in seven patients were affected and in patient one or more of the metatarsals were thickened. None of the 12 first meta- examined was involved. The high incidence of localization in the ulnas and rsals appears to be the most diagnostic feature of the skeletal lesions of poisoning excess vitamin A intake. In Case 3, metatarsal thickenings were not visible three after onset when ulnar hyperostoses were demonstrated, but 10 weeks after the wal of all vitamin A by mouth, both second metatarsals were found to be ed. There is no satisfactory explanation for the high frequency in the ulnas and sals; it is possible that trauma played some part in thickening these relatively hones. The bones at the roots of the extremities, the femurs and humeruses, which tively well protected from trauma by heavy muscles were the least affected. Only the 14 femurs and none of the 14 humeruses showed cortical thickening. The es and scapulas were normal in all patients. Five of 14 clavicles exhibited tical hyperostoses.

arliest roentgenographic observations were in Case 3 in which films showed yperostoses in the ulnas three weeks after the appearance of clinical swellings orearms. Early, the hyperostoses have a shell-like appearance with a zone of ed density between the subperiosteal thin layer of bone and the external surface l cortex. After withdrawal of vitamin A this intermediate clear zone disappears; ostoses then shrinks onto the old cortex and fuses with it (Fig. 9). These solid ortical thickenings are in turn gradually resorbed from within but remain r many months after complete clinical recovery. During the reparative phase e hyperostoses became lamellated.

ounts of vitamin A in the blood have been increased in all patients whose bloods tested. The concentrations varied from 400 to 2000 u./100 cc. It is not cer-

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tain how early blood vitamin A rises, or whether it is elevated during the long latent period prior to the appearance of clinical manifestations; it is possible, however, that an excess of vitamin A in the blood might point to the diagnosis while the patient was still asymptomatic. Following the stoppage of ingestion of excessive vitamin concentrate, vitamin A levels in the blood fell gradually and did not return to normal levels for several weeks (Case 5; Toomey,[7] Dickey[8] and Rothman[9]).

The rapid and complete clinical recovery of these patients after the stoppage of overdosage is one of the most distinct and convincing features of the syndrome. In patients observed personally, tenderness, pain, hyperirritability and anorexia have disappeared completely within one week. Recovery is comparable to the recovery in scurvy following the administration of vitamin C. In Case 1, recovery was so rapid after admission to the hospital that a bone biopsy which had been scheduled was cancelled.

As mentioned earlier, hypervitaminosis A has been confused by the author with infantile cortical hyperostosis. Personal communications from several sources indicate that this continues to be a not infrequent diagnostic error. Actually there are but two features which are common to both disorders; cortical hyperostoses and tender soft tissue swellings. In contrast, there are several outstanding differences which readily identify hypervitaminosis A and infantile cortical hyperostosis as separate entities. Infantile cortical hyperostosis has always made its appearance during the first four months of life and in one case was present on the first day of life; in hypervitaminosis A, on the other hand, diagnostic clinical signs have never been recognized prior to the 12th month of life. It is interesting that there is no recorded example of onset between the 5th and 11th months in either disorder. The face and jaw have been swollen and the mandible has been thickened in every case of infantile cortical hyperostosis; these structures have not been affected in a single case of hypervitaminosis A. Metatarsal hyperostoses have been present in every case of vitamin A poisoning in which the feet have been examined roentgenographically but have been demonstrated in only one case of infantile cortical hyperostosis. The blood vitamin A has been increased in hypervitaminosis A in every patient tested; blood vitamin A levels were normal in the only six patients with infantile cortical hyperostosis so tested. Fever is the rule in infantile cortical hyperostosis (15 of 17 cases); fever, other than transient fever due to respiratory infection, was absent in all cases of hypervitaminosis A.

Excessive intake of vitamin concentrate A and D preceded poisoning by vitamin A in all cases; vitamin intake has apparently not been excessive in any cases of infantile cortical hyperostosis. Also the feeding of excessive vitamin concentrate A and D during the first four months of life has not produced the manifestations of infantile cortical hyperostosis.[4,7,9] It seems likely that impaired absorption of vitamin A in oil during early life[10] is responsible for the absence of toxic symptoms in babies fed large amounts of oleum percomorphum during the first months of life. Recovery from vitamin A poisoning is dramatically rapid after admission to hospital and stoppage of the excessive ingestion of vitamin A; in contrast, the signs and symptoms of infantile cortical hyperostosis have continued and exacerbations have occurred weeks and months after hospital entry when it was certain that there was no excessive ingestion of vitamin A. Scapular lesions are unknown in vitamin A poisoning; they have been present in several cases of infantile cortical hyperostosis. Soft tissue swellings in the latter disease are usually much larger and more tender and the edges of the hyperostoses are much rougher than their counterparts in hypervitaminosis A.

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Summary and Conclusions

The clinical manifestations, the roentgenographic changes in the skeleton and the elevation of blood vitamin A are reported in a group of seven infants and younger children poisoned by ingestion of excessive quantities of vitamin concentrates A and D over periods of several months.

The differential features of vitamin A poisoning and infantile cortical hyperostosis are discussed.

Three types of vitamin concentrate A and D, commonly used in routine pediatric prophylaxis, were found to be toxic when ingested in sufficiently large quantities over sufficiently long periods. The minimal preclinical latent period of vitamin A poisoning was about six months and the minimal toxic daily dose was about 75,000 units.

Excessive dosage was due to overenthusiasm for vitamins and ignorance of the dangers of high vitamin intake.

The hazards of vitamin A poisoning from the routine prophylactic feeding of vitamin concentrates A and D to healthy infants and children on good diets are considerably greater than the hazards of vitamin A deficiency in healthy infants and children not fed vitamin concentrates.

Addendum

Since this manuscript was submitted for publication, two additional cases of vitamin A poisoning have been described (Fried, C. T., and Grand, M. J. H., Hypervitaminosis A, Am. J. Dis. Child. 79:475, 1950). The clinical, chemical and roentgen findings are all similar to those in the other reports. A total of 14 cases of infantile and juvenile poisoning due to vitamin A have now been recorded.

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Spanish Abstract

Envenenamiento Crónico Debido al Exceso de Vitamina A: Descripción de Manifestaciones Clínicas y de Roentgen en Siete Infantes y Niños Menores

Las manifestaciones clínicas, cambios roentgenográficos en el esqueleto, y la elevación vitamina A de sangre se reportan en un grupo de 7 infantes y niños menores envenenados por la ingestión de cantidades excesivas de concentrados de vitamina A y D por períodos de varios meses.

Se discuten las características diferenciales del envenenamiento de vitamina A y la hiperostosis cortical infantil.

Se encontró que tres tipos de concentrados de vitamina A y D, comunmente usados en la rutina pediatrica profilaxis, son tóxicos cuando ingeridos en cantidades suficientemente grandes durante periodos suficientemente largos. El periodo latente preclínico mínimo de envenenamiento de vitamina A fué de 6 meses y la dosis diaria tóxica mínima fué de poco más o menos 75,000 unidades.

La dosis excesiva fué debida al gran entusiasmo por vitaminas y a la ignorancia de los peligros de alta toma de vitaminas.

Los peligros del envenenamiento de vitamina A de la alimentación profilactica de rutina de concentrados de vitamina A y D a infantes y niños sanos que tienen buenas dietas son considerablemente más grandes que los peligros de la deficiencia de vitamina A en infantes y niños sanos que no estan alimentados con concentrados de vitamina.

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in London, England. It is our feeling that we have described a clinical syndrome and not necessarily a specific disease. This conclusion seems amply justified by virtue of the characteristic symptomatology, the roentgenologic appearance and the constant response to specific, although empiric, therapy.

Poisoning Due to Excess Vitamin A; Its Relation to Infantile Cortical Hyperostosis. DR. JOHN CAFFEY, New York.

The clinical, roentgenologic and chemical findings in 4 infants who had poisoning due to ingestion of large amounts of percomorph liver oil are presented. The long incubation period of approximately six months is emphasized, as well as the rapid subsidence of the clinical manifestations after withdrawal of percomorph liver oil.

The similarities and differences between poisoning due to vitamin A and infantile cortical hyperostosis are discussed. The absence of mandibular and scapular involvement, the later onset, the dramatic relief of symptoms after a few days' withdrawal of all types of vitamin A preparations and the history of chronic ingestion of vitamin A are the principal features of vitamin A poisoning which differentiate it from true infantile cortical hyperostosis. The similarity of the soft tissue swellings and roentgenologic findings in the skeleton in the two conditions is stressed. The question is raised whether a preparation potentially as dangerous as percomorph liver oil and other vitamin A concentrates should be marketed without more precautions than are used at present.

DISCUSSION

DR. HUGH W. JOSEPHS, Baltimore: Since my first report (Hypervitaminosis A and Carotenemia, AM. J. DIS. CHILD. 67:33-43 [Jan.] 1944) in 1944, I have had 4 more cases, 1 of which was sent in from outside. I want to show slides on these to you now. The picture may fill in some of the gaps. Clinically speaking, I have nothing much to add to what Dr. Caffey said. The importance of recognizing the condition, I think, is great. The condition may be much commoner than we have any idea of at present. [Slides]

DR. J. M. LEWIS, New York: It seems to me that there are more cases of hypervitaminosis A than there are instances of frank vitamin A deficiency, if we exclude those cases of vitamin A deficiency complicating diseases in which an interference exists with the absorption of the vitamin as, for example, cystic fibrosis of the pancreas and celiac disease. In other words, the danger of hypervitaminosis A appears to be greater than the possibility of development of vitamin A deficiency among normal infants and children. We have maintained through the years that supplementation of the diet with vitamin A products is superfluous for normal infants and children except in unusual circumstances when the child vomits frequently or refuses the major portion of its diet. Of course, children with steatorrhea and premature infants should receive vitamin A supplements, preferably in the aqueous preparations.

Most of the cases hypervitaminosis A have resulted from long-continued use of excessive doses (1 to 2 teaspoonfuls [5 to 10 cc.]) of a highly potent preparation (50,000 to 60,000 units of vitamin A per cubic centimeter). The possibility of vitamin A poisoning would be much more remote if the concentration of vitamin A in all preparations were standardized to 5,000 or 10,000 units per cubic centimeter. Furthermore, the size of the bottles should be restricted to a capacity of 10 or 15 cc. rather than 50 cc., as overzealous mothers would be less likely to give 1 to 2 teaspoons of a vitamin A preparation when the capacity of the bottle is only 10 to 15 cc. I think that, eventually, manufacturers will be required to meet regulations of this type.

DR. JOHN CAFFEY, New York: Dr. Josephs, none of these patients showed accelerated skeletal development. In experimental vitamin A poisoning with small animals, Wolbach found all features of bone growth accelerated, especially tabulation. I am in complete agreement with Dr. Lewis. There is no good reason a healthy infant or child taking a normal formula or diet should receive added concentrate of vitamin A. These preparations are needless, expensive and potentially dangerous in the hands of mothers for daily administration to healthy infants and children.

Hyaline-like Material in the Lungs of Newborn Infants: Its Incidence, Pathogenesis and Role in Fetal and Neonatal Mortality. DR. HERBERT C. MILLER and DR. M. HARRY JENNISON, Kansas City, Kan.

Evidence has been presented in an earlier study by Miller and Hamilton indicating that the "vernix membrane" in the lungs of newborn infants probably is the result of an injury to the epithelium lining the bronchioles, alveolar ducts and terminal air spaces and does not result from aspiration of the contents of the amniotic sac. The nature of the injury postulated in the investigation referred to was not determined, although the lesion in the lung of the newborn infant resembled those seen in older persons who died from pandemic influenza, acute pneumonias of coccic origin and rheumatic pneumonitis.

In the present study an investigation was made on 4,117 consecutive births to determine what, if any, clinical factors might help explain the pathogenesis of this pulmonary lesion. There were 66 fetal and 85 neonatal deaths among the 4,117 births; 28 of the 85 infants had lesions in their lungs.

Based on the postmortem examination of 71 of the 85 infants who died during the neonatal period, 27.5 per cent of all liveborn infants who weighed from 1,001 to 1,500 Gm. at birth had this hyaline material in their lungs, often in the form of a membrane. The incidence diminished to 11.1 per cent among infants weighing 1,501 to 2,000 Gm. and continued to decrease, so that in infants weighing more than 3,000 Gm. it was practical nonexistent. The lesion was also practically nonexistent among infants weighing less than 1,000 Gm. It rarely occurred in the lungs of stillborn infants. The pattern of distribution was the same in both white and nonwhite infants in the various weight groups.

The pulmonary lesion was more apt to be found among infants whose mothers had no serious complications of pregnancy and labor than among those whose mothers did. The lesion occurred less frequently among infants with some obvious clinical or anatomic explanation for their deaths than it did among infants who had none. These were significant differences.

If a liveborn infant in this series weighing over 1,000 Gm. at birth died during the first twenty-four or forty-eight hours of life and came to autopsy, there was a 65 per cent chance that the pulmonary lesion would be observed. The chances of observing the lesion at autopsy was increased to 90 per cent if there was no obvious clinical explanation for the baby's death and no serious maternal complication of labor or pregnancy. It was felt that the lesion was the sole cause of death in 11 of the 71 infants who had postmortem examinations and that it shared equally with other causes in 11 additional cases. The sex, order of birth, length of labor, the time that elapsed between rupture of the membranes and delivery,

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SUMMARY

Tubular reabsorption of water, according to the shifts in the endogenous creatinine clearance, is significantly increased following ingestion of dextrose in both the newborn and infants. In the first hours after delivery, tubular reabsorption of water may amount to as much as 99 per cent of the glomerular filtrate. In thriving infants a notable rise in the glomerular filtration rate occurs following a dose of dextrose and, at the age of 2 months, values according to body surface may attain normal adult figures. In atrophic and newborn infants, the amount of glomerular filtration is extremely low and does not vary significantly following ingestion of dextrose.

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HYPERVITAMINOSIS A

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AND
MILTON J. H. GRAND, M.D.
NEW YORK

HYPERVITAMINOSIS A is a clinical entity which occurs in late infancy and early childhood. The pathologic processes are the result of a prolonged and excessive intake of vitamin A and a derangement of vitamin A metabolism. Clinically, the condition is manifested by anorexia, with loss of weight, extreme irritability and fretfulness, low grade fever, pruriginous rash, sparseness of hair, hepatomegaly and exquisite pain on pressure over the long bones. Biochemically there are abnormally high vitamin A levels in the blood serum and increased levels of the serum lipids. Roentgenographically, the changes in the long bones are distinctive, characterized especially by periosteal proliferation.

A review of the literature uncovered a significant scarcity of these cases. The study of the effects of excessive dosage of vitamin A was limited to experimental animals, until Josephs'[1] case report in 1944 revealed the existence of a similar clinical entity in man. His patient was a 3 year old boy who had a voracious appetite for butter, hepatomegaly and sparse, coarse hair and whose serum vitamin A, serum lipid and serum phosphatase levels were elevated, while the serum proteins were depressed. Roentgenographically, he showed abnormalities of the long bones. The second case was reported by Toomey and Morissette[2] in 1947. Their case was similar to the one reported by Josepha. They added other features which further described the condition, i.e., localized periosteal swellings in the long bones and pain in these areas, with complete recovery from these phenomena when vitamin A was withdrawn from the diet. They were also able to repeat experimentally the clinical picture in this patient after the symptoms subsided

From the Pediatric Service of the Bronx Hospital, Dr. Bernard S. Denzer, director (retired).

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Am. J Dis. Child. 79:475-86, 1950

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by renewing the high vitamin A intake. Since these two reports, 2 additional cases were recorded in 1948 by Rothman and Leon.[1] Roentgenographically, they distinguished hypervitaminosis A from infantile cortical hyperostosis.

It is quite likely that the paucity of reports of cases of this syndrome is related more to the lack of its recognition than to its actual nonexistence. With the widespread and intensive use, in many children, of concentrates containing vitamin A and the early introduction of foods high in vitamin A and carotene content, it is surprising that many more instances of hypervitaminosis A have not appeared. However, other factors than simply the ingestion of large amounts of vitamin A may be involved in the pathogenesis of this clinical picture. These factors may be concerned with a faulty metabolism of the ingested vitamin, a dysfunction of the liver or disturbances in the facilities for storage, destruction or excretion of vitamin A. It is the aim of this report to reemphasize the existence of this syndrome in infants by presenting 2 additional cases, to discuss briefly the metabolism of vitamin A and to indicate its pathophysiologic aspects.

REPORT OF CASES

Case 1.—A. S., a boy 16 months of age, was referred to the pediatric service of the Bronx Hospital on March 28, 1947, because of protracted irritability and generalized muscle tenderness.

The child was normally born at term of a primiparous mother. The prenatal and postnatal periods were normal. The weight at birth was 7 pounds 12 ounces (3,515 Gm.). For the first five months, he was given breast feedings, followed by supplementary cow's milk mixtures. He received orange juice and cod liver oil in optimum doses from early infancy and gradually was introduced to a full regular diet. He walked at 10 months and erupted his first tooth at 7 months. The child was immunized against whooping cough, diphtheria and smallpox without any untoward effects.

The family history was noncontributory. The patient was well until "sometime between the 5th to the 6th month of age." The mother noted then that he was in a more or less constant state of irritability, incessantly rubbing himself as though from an "itch." This became progressively worse, until such time as excoriated areas appeared over the lower extremities and the face. Various forms of therapy were employed to alleviate the pruritus, all to no avail. This situation continued for several months with varying periods of remission and relapse. During all this time the general condition of the child remained good and normal development continued. However, periods of extreme irritability and crying occurred with increasing frequency and intensity. It was reported that at times the child would cry out vigorously as though in severe pain, and, if any attempt to comfort him

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was made, the crying and irritability became worse from what appeared to be the pressure of the touching hand. This phenomenon progressed to the point where the mother could not touch any part of the child without eliciting a period of fierce crying. About ten days prior to his admission to the hospital the infant had an episode of moderately severe vomiting followed by anorexia. Severe tenderness on pressure was noted over the upper and lower extremities. The feet became slightly swollen. Three days before his admission the child awoke with edema of the lips and eyelids which spontaneously disappeared in a few hours. Since the onset, there had always been a reddish desquamating, brawny eruption over the chest, upper arms, face and the lower portion of the legs. On the day before his admission the child had frequent loose stools and a "very dark" urine. All the systems reviewed were otherwise normal. Physical examination revealed a fairly well nourished and normally developed infant who seemed to be in pain. The face was anxious and expressed severe discomfort. Crying and irritability were prominently exhibited. The posture assumed by the child was oftener supine, with both upper extremities outstretched and immobile. However, when he was lifted from the supine position, he maintained himself for an adequate length of time to allow for feeding and other nursing care. It was significant that the arms were held in a more or less fixed position of extension. Palpation of the forearms elicited shrill cries of pain. Extending from the wrists to an area just below the elbows were fusiform swellings. The soft tissues overlying these swellings were tense but not edematous. The musculature offered no tonal quality especially on active or passive motion. Over the cheeks, forehead, abdomen and the outer surfaces of the arms and legs there was present a dry, fine, scaly, squamous type of cutaneous lesion with a brawny nonpitting edema. The latter was only slight. The lesion of the skin was dull reddish and was not inflammatory or raised at the edges. Scratch marks were evident throughout the involved skin areas. Except for an enlarged nontender liver 3 cm. below the right costal border the results of the remaining portions of the examination were essentially within normal limits.

The laboratory data were as follows: Repeated examinations showed the urine to be normal. Hemoglobin measured 12.8 Gm. per hundred cubic centimeters. Red blood cells numbered 4,860,000 and white blood cells 30,800 per cubic millimeter, with 21 per cent neutrophils, 1 per cent band forms, 1 per cent eosinophils, 74 per cent lymphocytes and 3 per cent monocytes. The sedimentation rate was 10 mm. at one hour, and the Wassermann and Kahn reactions were negative. Alkaline phosphatase measured 35 units; serum calcium, 10.3 mg.; serum phosphorus, 4.6 mg., and serum protein, 5.2 Gm., per hundred cubic centimeters. The blood vitamin C level was 1.6 mg. per hundred cubic centimeters. Urinary excretion of creatine and creatinine showed 2.46 Gm. of total nitrogen, with 41.3 mg. of creatine and 78.5 mg. of creatinine, per twenty-four hours. The creatinine coefficient (k) was 10.

Electrocardiographic studies were repeated and the tracings were observed to be normal.

On March 31, roentgenographic examination of the long bones disclosed periosteal thickening involving the shafts of the right and left ulnas at the midportions for about 2 cm.; the thickening gradually tapered off toward the ends of the

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bones. There was lateral bowing of the shafts of the lower extremities, with widening of the ends of the bones and slight arteresis. The epiphyses were irregular in outline (fig. 1). Three weeks later another roentgenographic examination of these same bones showed evidence of healing by the appearance of smoother epiphysial surfaces.

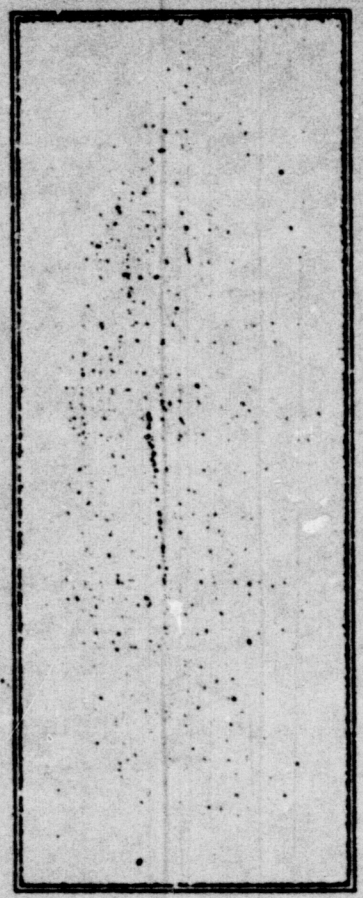

Fig. 1 (case 1).—Roentgenogram of long bone of lower extremity. Note irregular epiphyses, lateral bowing and widening of ends.

On April 2, electromyographic studies were carried out. At random the following muscles were examined: right tibialis anticus, right quadriceps, left semitendinosus and left gastrocnemius. The patient performed voluntary contractions in all these muscles except the right quadriceps during the tracings. These contractions were strongest in the right tibialis anticus, with amplitudes of 20 to 30 microvolts (fig. 2). The voluntary contractions of the left semitendinosus and left gastrocnemius were weaker, with amplitudes of 10 to 15 microvolts. Normal interference waves were absent in the tracings of all muscles, even in the right tibialis anticus during its strongest contraction. All the tracings showed the electromyographic pattern of the transitory stage. The left gastrocnemius showed single oscillations after five to ten seconds at any time of the transitory stage. These findings allowed the assumption of the presence of a slight neuromuscular disorder rather than a myogenic one.

On the second day of his admission a low grade fever (elevation of temperature to 101 F.) was noted. This persisted for four days, when the temperature fell to normal and was not again elevated during the entire stay in the hospital. The leukocytosis subsided, and the brawny, squamous eruption gradually faded. The severe pruritus became less and the irritability slowly disappeared. The general condition of the infant was much better, and clinically he was comparatively well. Except for a routine normal diet for a child of his age no therapeutic measure was employed. No vitamin preparation was given.

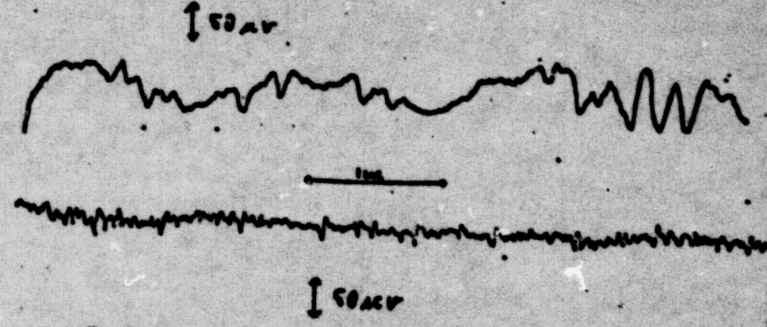

Fig. 2.—Electromyographic tracings: upper, contractions of right tibialis anticus (case 1); lower, contractions of biceps brachii (case 2).

At this point it was felt that infantile cortical hyperostosis could well have accounted for most of the features this child presented except for the elevated alkaline phosphatase and lowered serum protein. However, since the child was improving and the symptomatology was subsiding, he was discharged from the hospital on April 23, to be followed at home under the supervision of one of us (C. T. F.).

The patient did not reappear for many weeks. When, finally, he was brought for examination, the entire symptom complex was still quite evident. It was apparent now that some process other than infantile cortical hyperostosis was responsible for the condition. A thorough questioning of the mother on the subject of vitamin therapy revealed huge ingestion of vitamin A. When the infant was 2 weeks old, administration had been started of percomorph liver oil in doses of 30 drops daily. Over a period of several months this was gradually increased to 2 teaspoons (8 to 10 cc.) daily. Hence, he was receiving this daily dose for over a year. It now became clear why the child improved during his first stay in the hospital—simply because of the unwitting withdrawal of vitamin A. On July 8, 1947, the blood level of vitamin A was determined and found to reach

1,636 international units. The lack of cooperation did not permit readmission of the child into the hospital until July 31. During this interval vitamin A was withheld from the diet. Thus, on August 4, almost one month following the original determination of the vitamin A level in the blood, an absorption curve for vitamin A was made. By this time the fasting level was 294 international units. After ingestion of 65,000 international units of vitamin A, the recording of levels was repeated at three, six and nine hours; the readings were 465, 444 and 411 international units, respectively (fig. 3). This curve is normal except that a high fasting level for vitamin A is disclosed. The reactions to the galactose tolerance test and the cephalin flocculation test for hepatic function were both normal. Three

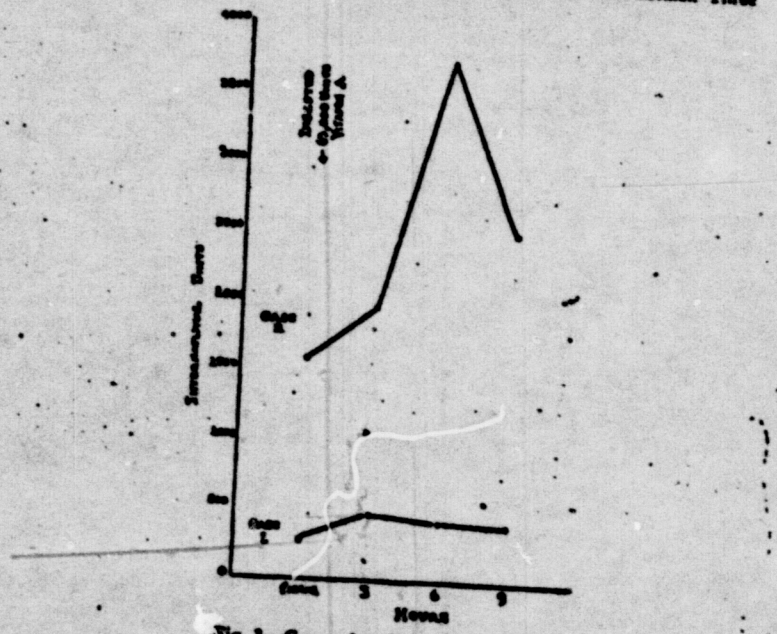

Fig. 3.—Curves for vitamin A absorption.

months later repeat roentgenograms showed complete resolution of the previous abnormalities.

CASE 2.—B. F., a white boy 2 years of age, was admitted to the Bronx Hospital on July 10, 1947, because of protracted and severe pain and tenderness of all four extremities.

On May 18, while playing on the street, he fell but sustained no injury other than a mild one to his nose with slight bleeding. At that time he repeatedly pointed to his legs and complained of pain. This was discarded by the mother as of little or no significance, until one week later she noticed that he winced with pain each time she clasped his left arm. Thinking this might be related to his previous fall, she consulted her physician, who assured her, after roentgenographic study of the arm,

that no bone injury was present. Since the child was complaining of generalized itching and a slight rash was present over both forearms, an antipruritic ointment was prescribed. The rash, itching and pain did not subside; in fact, in the course of the next week, all four extremities became painful and the rash and itching grew progressively worse. Concomitantly, irritability, which hitherto was slight, now caused explosive outbreaks of temper. Repeated visits to dermatologists resulted only in the assurance that the child would get well after the "allergic" symptoms subsided. The treatment in each instance was directed along antiallergic channels. The irritability, pruritus, pain, tenderness, crying, anorexia and associated loss of weight became so intense that further medical help was sought.

The boy was seen by one of us (M. J. H. G.) on July 10. At this time the past and family history did not reveal any contributory information; excessive ingestion of vitamin A was denied.

The physical examination disclosed a well developed, undernourished boy lying immobile and quietly in bed. He was covered with scratch marks over the extremities, back and chest. The facies was pinched and anxious and there was an expression of pain. The scalp hair was sparse and coarse. Gentle pressure over the extremities elicited outcries of excruciating pain. He cried incessantly during the examination, especially on palpation of the midportions of the extremities. The skin over these areas was brawny with a fine scaly type of eczematous lesion. This extended from the wrists to the elbows and from just above the ankles to the tibial tubercle, especially on the outer surfaces. The bony structures underlying these cutaneous lesions were distinctly enlarged in the transverse diameters and appeared somewhat bowed because of this swelling. The liver was enlarged 2 fingerbreadths below the right costal border. The remaining results of the examination were within normal limits. He was, therefore, immediately hospitalized with a provisional diagnosis of hypervitaminosis A or infantile cortical hyperostosis.

After his admission, the following laboratory data were disclosed: Repeated examinations revealed the urine to be normal. Hemoglobin was 9.8 Gm. per hundred cubic centimeters. Red blood cells numbered 4,000,000 and white blood cells 11,350 per cubic millimeter, with 55 per cent polymorphonuclear leukocytes, 40 per cent lymphocytes and 5 per cent monocytes. The erythrocyte sedimentation rate was 33 mm. in one hour. The Wassermann and Kahn reactions were negative. Total cholesterol in the blood was 217 mg.; nonprotein nitrogen, 32 mg.; serum calcium, 10.4 mg.; serum phosphorus, 4.8 mg., and serum vitamin C level, 0.5 mg. per hundred cubic centimeters. In a twenty-four hour sample of urine creatinine measured 144 mg. The spinal fluid had 2 lymphocytes per cubic millimeter and 15 mg. of protein and 105 mg. of sugar per hundred cubic centimeters. All cultures were sterile. The total serum protein was 6.5 Gm. per hundred cubic centimeters, with 4.4 Gm. of albumin and 2.1 Gm. of globulin. Alkaline phosphatase measured 26.0 units per hundred cubic centimeters. The reactions to the cephalin flocculation and the galactose tolerance tests were normal. Electromyographic study of the left quadriceps, semitendinosus and both recti abdominali muscles showed no abnormalities. Both biceps brachii showed normal interference patterns, with amplitudes from 30 to 80 microvolts. Hence, there was no reason to believe any neuromuscular disorder was present. Electrocardiographic studies showed normal findings.

Roentgenographic examination of the long bones showed periosteal thickening involving the middle third of the shafts of both tibiae, the left ulna and the lower part of the right ulna (fig. 4). The lower jaw, clavicles and scapulae showed no abnormalities.

In view of these findings vitamin A blood levels were determined. On June 20, the level was found to be 700 international units, on June 28, 1,400 international

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units and on June 30, 2,500 international units. Ordinarily, vitamin A is not excreted by the kidney in the human being unless the amount ingested is huge, and then only under abnormal conditions. The urine disclosed 1.3 international units per hundred cubic centimeters and the stool 24 international units per gram, which is normal. The curve for vitamin A absorption (fig. 3) was distinctly abnormal. The fasting level was exceedingly high, reaching 1,600 international units. Three hours after ingestion of 65,000 international units, the blood level was 1,976 international units; at six hours it reached 3,743 international units, and at nine hours there was a slight fall to 2,511 international units. All these findings were the highest blood levels ever to have been recorded for vitamin A.

The mother was again questioned, after these laboratory results were reported, and finally admitted that the child had been receiving ½ to ¾ teaspoon (2 to 3 cc.)

Fig. 4 (case 2).—Roentgenograms showing periosteal thickening of middle third of shafts of both tibias (*A*) and of lower part of right ulna (*B*).

of percomorph liver oil daily for many months, in addition to ingesting huge amounts of butter. It was found that on many occasions the child had raided the icebox and eaten from ¼ to ½ pound (113 to 226 Gm.) of butter at one session. The mother did not hesitate to use butter freely with all foods at all meals.

The case for hypervitaminosis A was now complete. Therapy consisted merely in complete withdrawal of carotene foods and vitamin A preparations. The child was discharged from the hospital on August 7. After this, he slowly made a complete recovery. Subsequent roentgenologic studies revealed normal bone structure. The hair became normal in texture and amount. The cutaneous lesion cleared and the symptom complex promptly vanished.

COMMENT

The extensive use of cod liver oil and its concentrates and the paucity of reports on any of their harmful effects in human beings may be responsible for the generally accepted opinion that the routine administration of cod liver oil in high dosage is harmless. This concept will have to be altered in view of the mounting evidence to the contrary. There is little doubt that many more human instances of hypervitaminosis A will appear in the literature in the near future. The awareness of the existence of the syndrome will greatly contribute to its earlier recognition.

The injurious effects resulting from the administration of excessive amounts of vitamin A have been observed and established in animals. Von Drigalski[1] administered 40,000 units a day to rats and reports the development of cachexia, rough skin, catarrhal conjunctivitis and diarrhea. Collazo and Sánchez Rodríguez[2] observed, in addition, exophthalmos and spontaneous fractures. Many other workers,[3] as cited by Clausen,[4] also observed injurious effects with the administration of varying amounts of cod liver oil. However, these workers used synthetic diets for their animals. Whether the results obtained were due to the absence of other protective substances in this type of diet or to toxic material in the oil used was not established. Moore and Wang,[5] using vitamin A in the purest available form as the crystalline vitamin A acetate, found it to be toxic when given in excess. The lesions involved the skeleton, muscles and skin. It is improbable that all the lesions were specific for hypervitaminosis A. In animals the characteristic lesions produced as a result of excessive vitamin A intake were skeletal fractures and hemorrhages. The fractures appeared consistently, while the hemorrhages were frequent but irregular in severity, distribution and incidence. The nonspecific changes often seen with excessive intake of vitamin A in a wide variety of oils were a rawness of the skin about the eyes, nose and mouth and a thinning and sparseness of the hair. A rapid loss of weight, diarrhea and emaciation were often part of the clinical picture. The association of bone changes and hemor-

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2. Collazo, J. A., and Sánchez Rodríguez, J. S.: Hypervitaminosis A, Klin. Wchnschr. 12:1732, 1933.

4. Clausen, S. W.: The Pharmacology and Therapeutics of Vitamin A, J. A. M. A. 111:144 (July 9) 1938. The Vitamins: A Symposium Arranged under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association, 1939.

5. Moore, T., and Wang, Y. L.: Hypervitaminosis A, Biochem. J. 30:2[illegible], 1945.

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ringes suggested a vitamin C impairment; however, no deviation of vitamin C blood levels was recorded in animals. The hemorrhages were cutaneous, intramuscular and uterine.[7] Light and his associates[8] found a hypoprothrombinemia in hypervitaminosis A which may account for the bleeding tendency.

Vitamin A accelerates a normal growth process in bone, and with excess dosage bone changes appear which are specific and constant. Wolbach[9] showed that excessive vitamin A profoundly affects the growth of bone and accelerates epiphysial cartilage cell sequences; the degree of acceleration of growth sequences bears a quantitative relationship to the amount of vitamin A administered. Mellanby[10] was of the opinion that vitamin A is not exactly a bone stimulant but rather a "controller" of certain growth elements, the coordinating activity of which is necessary for normal bone production. Moore and Wang,[7] using excessive dosage in animals, reported abnormal thinning of the cortex, with widening of the cancellous portion of the shafts of the long bones and a detachment of the epiphyses. In human beings, with excessive intake thinning and irregularities of the cortex, mottling of the epiphyses and periostitis have been reported.[11]

The primary organ concerned with vitamin A metabolism is the liver. Its capacity to store this vitamin is enormous,[12] and it can maintain 95 per cent of the total vitamin A reserve.[13] This storage in the liver is considered harmless. However, any amount which overwhelms the capacity of the liver to remove vitamin A from the blood is considered harmful.[14]

There is a tendency for each person to have a constant vitamin A blood level during health and under wide variations of intake.[13b] The regulation of the blood level of the vitamin is believed to be governed by the liver.[15] The mechanism for this control is suggested by the following: (*a*) the hepatic vitamin A level is directly proportional to the duration and intensity of the dosage[16]; (*b*) it is difficult to raise the plasma level beyond the normal maximum except for a few hours with excessive intake of vitamin A[17]; (*c*) the Kupffer cell may destroy the liberated excess vitamin A[18]; (*d*) the blood concentration of vitamin A is independent of the quantity stored in the liver and becomes related to the vitamin A level in the liver only after the hepatic stores have become depleted.[19] However, with excessive intake over a long period of time, abnormally high levels are obtained. Here the hepatic regulatory mechanism fails.[17] On the other hand, Josephs[1] cited the observation on an 8 month old infant who received 500,000 units of vitamin A daily over a period of four months and who at the end of this time disclosed no clinical evidence of toxicity and a normal vitamin A level in the blood of 110 units. Most of the children who are receiving excessive vitamin A through error or ignorance may follow this pattern, thus accounting for the meager number of case reports of human toxicity.

It becomes apparent that some factor must be involved in the production of toxic symptoms other than excessive dosage and duration of administration. This factor may reside in the liver. Davies and Moore demonstrated that death may occur in hypervitaminemic rats even though there is room for considerable hepatic storage of vitamin A.[12a] Fatty infiltration is found in the Kupffer cells of hypervitaminemic animals.[20] These observations suggest that supersaturation of the liver is not alone responsible for the toxic manifestations. Clinically, all the reported instances of this disease disclose hepatomegaly. However, the laboratory data indicate no consistent findings of hepatic dysfunction. Abels and his co-workers[21] showed that a derangement in one hepatic function does not necessarily involve other functions of the liver. This may possibly explain the normal values for hepatic function in both our cases. Since a specific hepatic function test for abnormal vitamin A metabolism is not available, the nature of the faulty

8. Light, R. A.; Alscher, R., and Frey, C. W.: Vitamin A Toxicity and Hypoprothrombinemia, Science 100:225, 1944.

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13. Moore, T.: Vitamin A and Carotene: VII. The Distribution of Vitamin A and Carotene in Body of Rat, Biochem. J. 25:275, 1931.

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15. Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, A.: Vitamin A Requirements in Rats, J. Nutrition 23:351, 1942.

16. Josephs.[1] Lewis and others.[15] Josephs.[14c]

17. Lewis and others.[15] Josephs.[14c]

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21. Abels, J. C.; Gorham, A. T.; Eberlin, S. L.; Halter, R., and Rhoads, C. P.: Hepatic Vitamin A in Rat as Affected by the Administration of Dibenzanthracene, J. Exper. Med. 76:143, 1942.

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process must await evidence of pathologic involvement in human liver. Assuming, then, that the fault lies in a deranged hepatic function, the curve for vitamin A absorption should reveal evidence of decreased hepatic tolerance. This is borne out by the curves shown in figure 3. In the first case the test was performed one month after withdrawal of the vitamin. Though the fasting level was still high, the liver had recovered sufficiently to absorb the excess dose given. In the second case, the test was done at the height of the illness, and the liver was incapable of metabolizing the excess dose. This, then, resulted in a high fasting level and an even higher level over the nine hour period, with failure to return to the base.

Since biopsy specimens of muscle in the cases of infantile cortical hyperostosis [22] disclosed degeneration with fatty and fibrous replacement as seen in muscular dystrophy or denervated muscle, electromyographic studies were done in both children (fig. 2). No uniformity of findings was encountered to indicate related neuromyogenic disease.

In the 2 cases herein reported, the criteria necessary for establishing a positive diagnosis of hypervitaminosis A were met. These are (1) a history of excessive intake of vitamin A over a prolonged period, (2) a symptom complex which is consistent with reported findings in animals and human beings, (3) a gradually complete recovery after withdrawal of vitamin A, (4) roentgenographic bone changes which are similar to those resulting from excessive administration of vitamin A in animals and (5) elevated vitamin A levels in the blood serum which are the highest recorded in the literature.

SUMMARY

1. Two classic cases of hypervitaminosis A are reported.

2. Hepatic dysfunction is suggested as the basis for the pathogenesis of this syndrome rather than supersaturation of the liver with vitamin A.

3. Curves for vitamin A absorption are shown as evidence of hepatic dysfunction.

4. The highest blood serum levels ever reported for vitamin A are recorded.

5. Electromyographic tracings are presented.

Dr. J. M. Lewis, of Beth Israel Hospital, and the Nutrition Laboratory of the Mount Sinai Hospital made the vitamin A determinations herein reported.

1220 Grand Concourse (Dr. Fried).

1040 Grand Concourse (Dr. Grand).

22. Smyth, F. S.; Potter, A., and Silverman, W.: Periosteal Reaction, Fever and Irritability in Young Infants: New Syndrome? Am. J. Dis. Child. 71:333 (April) 1946.

MYOCARDITIS FOLLOWING MEASLES

Report of a Case

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AND

DONALD C. NILSSON, M.D.

BROOKLYN

INFORMATION relative to the incidence of cardiac complications following measles is extremely limited, possibly because such cases have not been reported in the past or because the disease is considered so frequently a mild infection that medical care is not sought. Particularly, is this true of the more serious abnormalities of cardiac function, such as myocarditis and heart block. We could find but 3 instances of the latter in the literature.

Eyster and Middleton [1] were able to find 1 case suggestive of measles causation in their review of the literature from 1896 to 1919. Lyon [2] later reported a case of permanent heart block in a 41 year old patient unquestionably originating at the time of an attack of measles. Recently, Clark [3] reported 3 cases of complete heart block possibly attributable to measles.

The purpose of this paper is to record an instance of varied and serious disorders of cardiac rhythm following measles.

REPORT OF CASE

V. F., a 5½ year old child of Italian extraction, was admitted to the Long Island College Hospital for the first time on May 26, 1948, because of abdominal pain and vomiting of twenty-four hours' duration.

The past history revealed that the child had been well except for occasional intestinal upsets, whooping cough at 10 months and rubella at 13 months of age. There was no history of rheumatic fever. The family history was irrelevant.

Thirteen days prior to his admission the patient had typical symptoms of moderately severe measles. One week was required for subsidence of the rash, anemia and fever, but serious anorexia and listlessness persisted until his admission to the hospital.

*From the Department of Pediatrics, Long Island College Hospital and Long Island College of Medicine.

1. Eyster, J. A. E., and Middleton, W. S.: Auriculoventricular Heart Block in Children, Am. J. Dis. Child. 19:13 (Feb.) 1920.

2. Lyon, E.: Right Bundle Branch Block Following Measles, Acta med. orient. 5:400, 1946.

3. Clark, N. S.: Complete Heart Block in Children: Report of Three Cases Possibly Attributable to Measles, Arch. Dis. Childhood 23:156, 1948.

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J. A. M. A. Sept. 23, 1944 V-1944 E186

7. When the angle between the vertical and horizontal arms is increased the operating team may have more room to work in the head, face or neck without compromising the anesthetist's access to the upper portion of the respiratory tract.

8. If the upper limbs of the drapes require angling to provide satisfactory operative exposure, one of the horizontal arms can be moved upward or downward to fit the need.

9. The frame is adjustable for lateral or posterior craniotomy exposures.

10. For lateral or posterior-lateral thoracotomy exposure the extended arm can be securely supported by tying it to the transverse sections of the frame.

HYPERVITAMINOSIS A

Report of a Case

TYREE C. WYATT, M.D.
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Syracuse, N. Y.
and
M. ELIZABETH FLETCHER, M.D.
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Hypervitaminosis A was first described by Josephs[1] in 1944. Toomey and Morlarie[2] reported a similar case in 1947 and presented evidence that the symptom complex was the result of hypervitaminosis A and not hypervitaminosis D. Two additional cases were reported in 1948 by Rothman and Leon,[3] who emphasized the roentgen observations. Since the patient of this report was examined by us, Dr. John Caffey reported 7 additional cases at the 1949 annual meeting of the American Pediatric Society.

SUMMARY OF PREVIOUS REPORTS

Clinical Features.—In previously reported cases the ages of the 4 patients were 3 years, 23 months, 14 months and 22 months. The parents in each case were extremely concerned about adequate vitamin administration, and in each instance there was a history of excessive dosage with vitamin concentrates. The predominant symptoms were anorexia, irritability, generalized pruritus and painful extremities, with a reluctance to stand or walk. Two children had repeated infections of the upper part of the respiratory tract. There was a uniform similarity in physical observations: All children showed a yellowish pallor, sparse coarse hair, dry scaly lips with bleeding fissures at the corners of the mouth and dry excoriated skin. There was tenderness over the long bones and generalized weakness. In 3 children the liver was slightly enlarged, smooth and firm on palpation.

Roentgen and Laboratory Observations.—Roentgenograms revealed "considerable irregularity in cortical structure"[1] and periosteal elevation with a single layer of subperiosteal new bone formation along the midportions of the shafts of the long bones. The ulna was the most frequent site of involvement. Next in order of frequency of involvement were the clavicle, femur and tibia. The important laboratory result uniformly obtained in all 4 cases was a significant elevation of the serum vitamin A level above the accepted normal value. In 2 cases the serum alkaline phosphatase level was increased above normal, and in 2 cases high normal values were present. All children showed a slight to moderate degree of anemia. The erythrocyte sedimentation rate was increased in 2 cases, normal in 1 and undetermined in the fourth.

REPORT OF CASE

History.—B. S., a white girl 3 years of age, was admitted Aug. 24, 1948 to the pediatric service of Syracuse Memorial Hospital with anorexia, tenderness of the extremities, low grade fever, weakness, pronounced irritability and severe generalized pruritus and scratching, especially severe in the lower extremities; symptoms were of two weeks' duration. The child felt that she could not walk properly and described a sensation of "walking on stones." She cried whenever the mother attempted to pick her up. Her past history included frequent infections of the upper part of the respiratory tract but no childhood diseases. Feeding in infancy had consisted of evaporated milk formula with the addition of the usual vitamins, cereals and vegetables. The child was immunized against diphtheria, tetanus, whooping cough and smallpox during the first year. The family history was noncontributory.

Significant Physical Observations.—The skin was pale and sallow, with severe excoriations of the legs and back. There was mild cervical adenopathy. The arms were decidedly tender, and in addition the patient exhibited generalized weakness, extreme irritability and unsteadiness of gait.

Laboratory Data.—The complete blood count on admission was essentially normal. Ten days later the white blood cell count was 14,900, with a normal differential. The urine was normal on repeated examinations. The erythrocyte sedimentation rate (Wintrobe) was 36 mm. in one hour. The hematocrit was 40 per cent, the icterus index 5. Cerebrospinal fluid from a lumbar puncture was normal. Throat cultures were negative for hemolytic streptococci and diphtheriae. Stool examination showed no parasites. Reactions of spinal fluid and blood to the Wassermann test were negative. Heterophil antibody titers were within normal limits. The Mantoux test with 0.1 mg. of old tuberculin was negative. Roentgenograms of the chest and abdomen showed no evidence of abnormality. Roentgenograms of the long bones revealed changes in both ulnas (see the accompanying figure). These consisted of elevation of the periosteum with subperiosteal new bone formation along the medial aspect of the midportion of the shafts. The metaphyses and epiphyses appeared normal.

Progress in the Hospital.—After the child was in the hospital ten days there was improvement of the pruritus and less irritability. The weakness and unsteady gait appeared less pronounced. Treatment during this period consisted of sedation, local treatment for pruritus and administration of vitamin B complex. The child was discharged eighteen days after admission, moderately improved, with a diagnosis of periostitis and generalized pruritus of unknown causation.

Progress Since Discharge from the Hospital.—The child was an office patient on Sept. 20, 1948, nine days after her discharge from the hospital; she exhibited essentially the same clinical condition as she did on leaving the hospital. There was slight excoriation of the skin and a slight infection of the upper part of the respiratory tract. The erythrocyte sedimentation rate was now normal. The blood values were normal except for a total leukocyte count of 14,020 with normal differential count. During the following week pruritus, irritability and weakness increased. In addition, it was noted that the patient's hair was becoming sparse. After she left the hospital there was pronounced loss of hair on the sides of the head anterior to the ears and bilateral recession of the hair line along the forehead. The remainder of the hair was thin and dry. At this time the pronounced similarity between this and the reported cases of hypervitaminosis A became apparent to us. On questioning the mother, it was learned that the patient had been receiving approximately 400,000 to 500,000 units of vitamin A and 60,000 to 70,000 units of vitamin D daily in the form of percomorph liver oil since 14 months of age, a period of almost two years. Serum vitamin A determination done at this time[4] revealed 127 micrograms (423 units) per hundred cubic centimeters, as compared with a normal range of 15 to 60 micrograms (or hundred cubic centimeters.[5] The alkaline phosphatase level was 7.2 Bodansky units. Roentgenograms of the long bones showed a slight increase in the periosteal reaction in the ulnas. The other bones remained normal in appearance. After discontinu-

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From the Pediatric Department of Syracuse University College of Medicine and Syracuse Memorial Hospital (Drs. Wyatt and Casabella) from the Department of Roentgenology, Fallon Clinic, Worcester, Mass. (Dr. Fletcher).

1. Josephs, H. W.: Hypervitaminosis A and Carotinemia, Am. J. Dis. Child. 67:33-43 (Jan.) 1944.

2. Toomey, J. A., and Morlarie, R. A.: Hypervitaminosis A, Am. J. Dis. Child. 72:318-340 (Nov.) 1947.

3. Rothman, P. A., and Leon, E. E.: Hypervitaminosis A, Radiology 51:368-376 (Sept.) 1948.

4. Dr. Daniel Robert, Department of Biochemistry, Syracuse University College of Medicine, made the test.

5. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, ed. 12, New York, The Blakiston Company, 1947, pp. 1068-1069.

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[illegible] of the preexisting liver oil dosage the pruritus subsided within a few days. Dyspnea, irritability and weakness disappeared rapidly, and within a month recovery was apparently complete. Roentgenographic examination of the long bones on May 28, 1949, revealed that both ulnas were normal.

COMMENT

In reviewing the cases reported previously it is noteworthy that the correct diagnosis was usually made in retrospect after additional history was obtained (perhaps with difficulty) from

Periosteal elevation and thickening along the shafts of both ulnas.

the parents. This point was emphasized by Dr. J. M. Lewis,[6] who related the difficulty he experienced in getting a mother to admit the administration of large doses of vitamin A to her baby. However, with the persistent extremely high vitamin A concentrations in the plasma (700 U. S. P. units per cubic centimeter) as well as roentgenographic changes in the long bones, he was convinced of the likelihood of hypervitaminosis A and finally obtained admission that the infant had received 1 to 2 teaspoons (5 to 10 cc.) of vitamin A and D concentrate for several months.

The members of the medical profession have long been concerned with the diseases resulting from insufficient vitamin intake. Recently we have appreciated the serious dangers of overdosage with vitamin D. We are now seeing cases of disturbed physiologic conditions following excessive dosage of vitamin A. Fortunately, recovery has been prompt and apparently complete on the withdrawal of the vitamin. In experimental animals lethal doses of vitamin A have been administered. In man the possibility of permanent hepatic damage must at least be considered.

Administration of large doses of vitamin A may be well tolerated for long periods of time. When it is ingested in large quantities it is rapidly removed from the blood and stored in the liver, maintaining normal blood levels. Hypervitaminosis A has not been produced in controlled cases of excessive vitamin A administration over a period of several months. This observation led Josephs[1] to suggest that in patients in whom clinical hypervitaminosis A develops there may be either an intrinsic alteration in the regulatory mechanism of vitamin A storage and metabolism or an alteration that is a consequence of vitamin A overdosage. Others have suggested that clinical hypervitaminosis A develops only after the liver is loaded with the vitamin so that it is no longer able to remove from the circulation the excessive amount ingested.

The etiologic basis of the clinical observations in hypervitaminosis A is still obscure. The skin and hair changes in man and experimental animals are suggestive of vitamin A deficiency. Josephs[1] suggests that the elevated phosphatase level, which is probably responsible for the bone changes, may be secondary to [illegible] damage produced by overdosage with the vitamin.

SUMMARY

A case of probable hypervitaminosis A has been reported. The clinical observations followed remarkably those described previously in 4 patients by Josephs, Toomey and Rothman. In this condition the symptoms subside dramatically when the vitamin is withdrawn, although the abnormal results of laboratory and roentgen studies may persist much longer.

TEMPORARY BALDNESS DUE TO COLD WAVE THIOGLYCOLATE PREPARATIONS

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and
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St. Louis

Among the millions of cold wave permanents containing thioglycolate which have been used by women at home and in beauty salons there have been only a few with deleterious effects on the skin and scalp. For the most part these have been considered due to primary irritation from the use of the ammonium salts of thioglycolate, and rarely to eczematous hypersensitivity. The dermatitis is usually found on the forehead, ears and nuchal regions. Fragmentation and splitting of the hair are not uncommon.

We are reporting two cases of temporary baldness following the use of cold permanent waves containing ammonium thioglycolate. The two cold wave permanents were given in

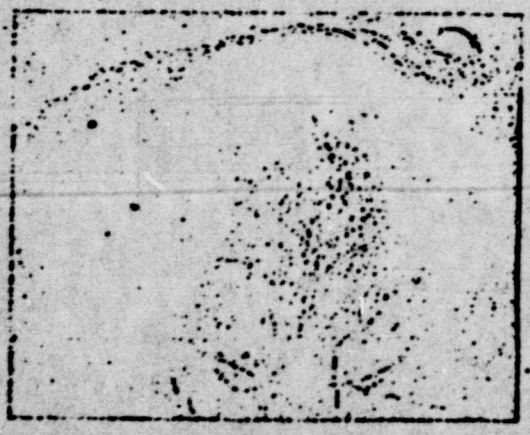

Fig. 1 (case 1).—View of frontal region of scalp showing partial hair loss with fragmentation of hair.

different beauty parlors, and two different commercial preparations of ammonium thioglycolate were used. The first patient began to have a regrowth of hair in approximately three weeks; the regrowth of hair in the second woman was visible after twenty days.

6. Lewis, J. M.: Personal communication to the author.

7. Wolbach, S. B.: Vitamin A Deficiency and Excess in Relation to Skeletal Growth, J. Bone & Joint Surg. 20:171-192 (Jan.) 1938. Bird, C. H., and Taylor, N. B.: Vitamin A Storage, in Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1943, pp. 637-651.

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HYPERVITAMINOSIS A

Report of an Unusual Case with Marked Craniotabes

By JAY M. ARENA, M.D., PAUL SARAZEN, JR., M.D., AND GEORGE J. BAYLIN, M.D.
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GRIBETZ[1] and his associates have recently reported two children with hypervitaminosis A and at the same time summarized the clinical and laboratory findings of the previous 14 reported cases. The following diagnostic criteria were brought out: the most common presenting symptoms were irritability, anorexia, loss of hair, pruritis, tender extremities producing disturbances in gait, and painful soft tissue swellings. Roentgenograms revealed cortical thickening involving the long bones, particularly the ulnae. The diagnosis is confirmed by finding a high plasma vitamin A level and obtaining a history of excessive vitamin A intake. Although all the cases reported in the literature were over one year of age, many of these infants had symptoms of hypervitaminosis A for several months before the correct diagnosis was established.

The following case report is that of an infant with severe symptoms of hypervitaminosis A including marked craniotabes as a predominating symptom.

REPORT OF CASE

L. E. B., a white female 6½ mo. of age, was admitted to Duke Hospital because of softening of skull and a lump on R foot.

Patient was delivered by cesarean section of a 37 yr. old primipara because of uterine inertia. Pregnancy had been uncomplicated and labor began spontaneously at term. Infant was normal at birth, weighing 3.5 kg. She was put on a standard evaporated milk formula. Because of a large anterior fontanel, more than average doses of vitamins were prescribed although no evidence of craniotabes was found at birth. Oleum percomorphum®* 10 drops twice daily and ABDEC®† 10 drops once daily were given from birth to 4 mo. of age.

Daily dosage was approximately 30,000 U.S.P. u. of vitamin A and 3,600 U.S.P. u. of vitamin D. She always ate well, gained weight satisfactorily and developed normally.

At 4 mo. of age, additional vitamins were prescribed because the fontanel was not closing. Oleum percomorphum® was then given in doses of 20 drops 3 times daily in addition to ABDEC® 10 drops daily. Daily dosage from 4th mo. on was approximately 80,000 U.S.P. u. of vitamin A and 11,000 U.S.P. u. of vitamin D. Two months later, at 6 mo. of age, a swelling was noted on lateral aspect of R foot. Marked craniotabes was discovered at the same time. Extreme irritability and anorexia became dominant symptoms. ABDEC® drops were increased to 15 daily, and oleum percomorphum® was continued at 20 drops 3 times daily. RGs were taken and a tentative diagnosis

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(Received for publication July 10, 1951.)

* Oleum percomorphum (Mead Johnson Company) is composed of the liver oils of percomorph fishes with viosterol and other fish liver oils. It contains vitamin A 60,000 u. and vitamin D 8,500 u./gm.

† ABDEC drops (Parke, Davis & Company) is a water-miscible, nonalcoholic, multivitamin supplement. It contains vitamin A, 5,000 U.S.P. u., vitamin D 1,000 U.S.P. u., vitamin B_1 1 mg., vitamin B_2 0.4 mg., vitamin B_6 1 mg., pantothenic acid 2 mg., nicotinamide 5 mg. and vitamin C 50 mg./0.6 cc.

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FIG. 1. Hyperostoses of inferior portions of both clavicles, most marked on right.

of infantile cortical hyperostosis was made. Three days before admission patient's foot was noted to be tender, and L arm was tender on moving. No history of injury or of fever. Patient was so irritable and suffered such pain on movement that she was carried about on a pillow and in such a manner she arrived on the ward.

Examination: Temperature was 38° C., PR 160/mm. Respirations 22/mm. Weight 7.5 kg. Head measured 47 cm. in circumference. Crown-to-heel length was 73 cm. Chest circumference was 43 cm. Entire skull was extremely soft. Characteristic "ping-pong ball" sensation was felt in all areas of the skull. In some areas, particularly about the anterior fontanel, so much softening had occurred that the skull felt more like a stiff membrane than bone. It was impossible to outline the anterior fontanel by palpation. There was a bony fusiform swelling at distal end of 5th metatarsal of R foot but no soft tissue swelling. Particular pain was produced when L upper extremity was moved. Liver was felt 2 cm. below R costal margin. Remainder of examination was normal.

Laboratory Data: Hgb. 12.4 gm./100 cc.; RBC count was 4.2 million/cmm.; WBC count was 5.0 thousand/cmm. with normal differential count. Stippling was not seen on examination of a fresh preparation of red blood cells. Blood serology was negative. Old tuberculin skin test 1:1,000 was negative. Blood chemistry showed Ca 10 mg./100 cc., P 5.9 mg./100 cc., alkaline phosphatase 17.9 Bodansky units, total proteins 6.8 gm./100 cc., with 3.5 albumin and 3.3 globulin. Plasma vitamin A was 257 µg./100 cc. (normal 30-60). Plasma carotene was 267 µg./100 cc. (normal

90-300). RGs: "Films of skull show thin bones throughout. Mandibles show normal bone detail. Ribs are normal. Right clavicle shows evidence of hyperostosis along inferior border, especially along lateral half. Hyperostotic bone is dense so that it blends in with normal cortical bone. There are similar changes in L clavicle, but of a lesser degree (Fig. 1). Films of femora show normal density with smooth contour cortices. However, there is slight irregularity along metaphyseal plates bilaterally which is not typical of any particular abnormality. Epiphyseal bone is normal. Tibiae and fibulae show normal density except that metaphyseal plates are somewhat denser than usual, but perfectly smooth and regular. Films of feet show on R side very definite hyperostosis of 4th and 5th metatarsals (Fig. 2). Change is characterized by being less dense than normal cortex with somewhat hallooned characteristics leaving a zone of decreased density between outer rim of hyperostotic bone and normal cortex. Other bones of the feet are normal. Films of arms show humeri normal. Both radii show dense

FIG. 2. Hyperostoses of R 4th and 5th metatarsals.

metaphyseal plates with no other changes. Left ulna shows a definite zone of hyperostosis at distal portion on radial side (Fig. 3). Metacarpals are normal. Distal ends of both ulnae are slightly denser than normal and not as regular as usual."

Hospital Course: Patient was afebrile. All vitamin preparations were withheld from time of admission. She rapidly became less irritable and took her feedings better during latter part of her week's stay in hospital. Pain on motion of extremities decreased and skull was firmer. She was discharged on a standard formula and diet with vitamin supplements of vitamin D 1,000 u. daily.

Patient was seen again 2 mo. after discharge from the hospital. She was remarkably improved and at that time her development, appetite and weight gain were normal with no irritability or painful extremities since discharge. She weighed then 9.2 kg. Anterior fontanel measured 6 × 7 cm. Craniotabes was not demonstrable. Swelling of R 5th metatarsal could not be felt. Laboratory studies showed alkaline phosphatase 3.1 Bodansky units, plasma vitamin A level 58 µg./100 cc. and plasma carotene level 304 µg./100 cc. RGs showed: "Films of skull show bones to be thicker and denser than before. Films of lower extremities show normal bones throughout. Feet were not included. Restudy of upper extremity shows restoration of normal metaphyseal detail, and previously described ulnar hyperostosis is no longer obvious (Fig. 4). Although bone density in general seems reasonably normal on original films—by comparison with the later studies it is quite obvious that there was originally a generalized, although slight, decrease in bone density associated with slight coarseness in architecture.

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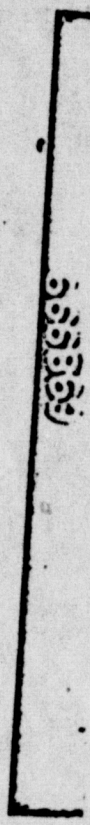

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None of this is evident in the later films. These interesting bone changes are, in the hyperostotic aspect, typical of hypervitaminosis A."

Patient returned for re-examination at age of 13 mo. Again no abnormalities were found. Growth and development were proceeding normally. RGs of clavicles and R metatarsals overlooked on previous examination were taken. They showed complete clearing of previously described hyperostoses.

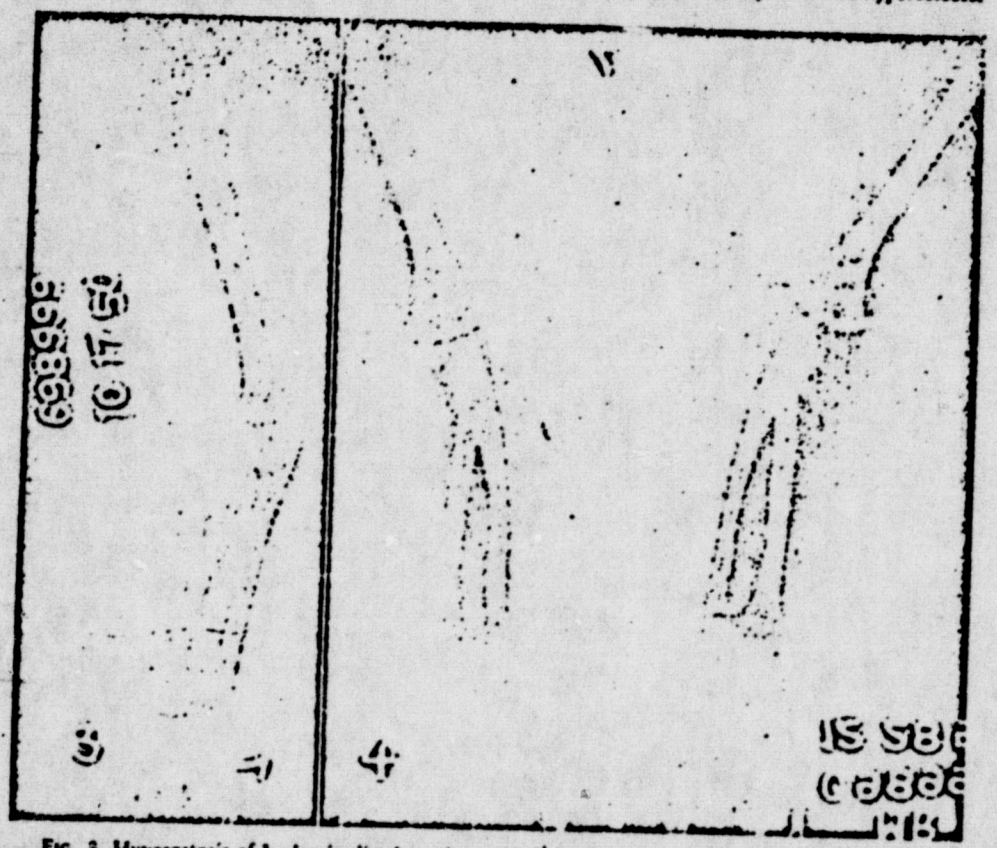

FIG. 3. Hyperostosis of L ulna in distal portion on radial side.

FIG. 4. Two months after withdrawal of vitamin A showing absence of previously noted ulnar hyperostosis on left.

DISCUSSION

Moore[2] and later Wolbach,[3] investigating the effects of hypervitaminosis A in rats and guinea pigs, found that there was a speeding-up of the metabolism of epiphyseal cartilage cells which resulted in their rapid maturation, degeneration and death. There was an increase in epiphyseal bone formation, and the shafts of the bones were being reinforced with bone from the epiphysis and from appositional bone growth. However, the resorption of bone was greater than its formation, and a resultant lag of calcification occurred which produced fractures from ordinary stress and strain. There were no histologic changes in the thyroids, parathyroids, adrenals or pituitaries of the laboratory animals that could explain the bone changes that were found.

The clinical course of hypervitaminosis A differs markedly from that seen with hypervitaminosis D,[4] although some of the symptoms may be identical. In hypervitaminosis D

the symptoms are more acute and consist of a sudden onset of severe anorexia, nausea, vomiting, thirst and constipation. The infants become progressively dehydrated, irritable, depressed and drowsy. Abdominal pain, muscle cramps, pallor, weight loss and finally stupor ensue. The blood pressure is elevated, there is moderate fever occasionally, and evidence of renal damage is present. The serum calcium and phosphorus are elevated in practically all cases. Accessory clinical findings include an elevated sedimentation rate, leucocytosis and anemia. In nonfatal cases vomiting ceases in 8 to 15 days after withdrawing vitamin D. Renal function returns to normal in 2 to 4 weeks, but the blood pressure may be elevated as long as 6 months. Serum calcium and phosphorus levels return to normal slowly. In more serious cases recession is slower, and relapses occur. Nervous symptoms may be present, such as hypotonia, loss of equilibrium and insomnia. Occasionally muscle twitchings occur, and rarely convulsions. When death occurs it is the result of uremia or brain hemorrhage. Treatment consists of discontinuance of administration of vitamin D, exposure to sunlight, milk feeding and use of any other foods of high calcium content. Bad prognostic signs are high blood pressure or increased nitrogen retention. High serum calcium and phosphorus levels are not necessarily alarming. Pathologically there is a widespread metastatic calcification involving the pancreas, lungs, synovia, dura, gastric mucosa, heart and blood vessels, subcutaneous tissue and the kidney tubules.

In the past, and probably to some extent at present, hypervitaminosis A has been confused with infantile cortical hyperostosis. Caffey[5] pointed out that there are only two similarities between the two conditions. These similarities are cortical hyperostoses and tender soft tissue swellings. On the other hand, there are many features which separate the two entities. Infantile cortical hyperostosis occurs during the first four months of life, occasionally even being present at birth, while hypervitaminosis A rarely occurs before the twelfth month. The mandible has been involved in every case of infantile cortical hyperostosis, whereas it has never been reported involved with hypervitaminosis A. Lesions of the metatarsals are constant with hypervitaminosis A, but only one case of infantile cortical hyperostosis has shown such involvement. Lesions of the scapula are unknown in hypervitaminosis A, but occur occasionally in infantile cortical hyperostosis. Soft tissue swellings in infantile cortical hyperostosis are larger and more tender than those with hypervitaminosis A. Fever is a prominent symptom in infantile cortical hyperostosis, but is absent with hypervitaminosis A unless a secondary infection is present. Vitamin A plasma levels are always elevated markedly in hypervitaminosis A, while they have been normal in those cases of infantile cortical hyperostosis in which they have been studied. A history of excessive intake of vitamin A is constantly present in cases of hypervitaminosis A and absent in those of infantile cortical hyperostosis.

Craniotabes may occur in a variety of conditions, such as rickets, hydrocephalus, osteogenesis imperfecta and congenital syphilis. A congenital type[6] has also been described. When craniotabes is seen as an early manifestation of rickets, there is softening along the suture lines of the squama of the occiput, of the posterior parts of the parietal bones, and along the borders of the large fontanel. In these areas finger pressure causes indentation of the bone with resiliency resembling a ping-pong ball. The soft areas have a parchment-like consistency at times. This picture is seen in the first few months of life when the rachitic process begins. The craniotabes may disappear before the end of the first year, even though the rachitic process continues. Examination reveals the presence

of congenital craniotabes in 10 to 35% of all newborn infants. Premature infants have a higher incidence than those born at full term. Congenital craniotabes, however, has not been found in infants born after breech presentation; so the thinning may be due to intrauterine pressure against the maternal pelvis. Chemically there is a diminished calcium and phosphorus content at the site of the porotic bone. Probably the condition is caused by discrepancy between rapid growth of brain and calcification processes in the vertex in the last month of gestation. It is associated with a generalized osteoporotic process in the newborn infant. However, it is not associated with clinical, radiologic or chemical manifestations of rickets; moreover, the softness is limited to areas proximal to the sagittal suture and does not occur in the lateral parietal areas as it does in rickets. Congenital craniotabes occurs twice as frequently in Negroes as in white infants. It usually disappears in the first few months of life, but must be differentiated from lacunar skull and osteogenesis imperfecta. The condition may be related to deficient maternal diet and intake of vitamin D during pregnancy, since there is an inverse relationship between the amount of sunlight exposure to the mother while pregnant and its incidence.

When vitamin A is ingested in large doses, it is rapidly removed from the blood and stored in the liver, maintaining normal blood levels. It is, therefore, not unusual that large doses of vitamin A may be well tolerated for long periods of time. Josephs[7] reports that the toxic effects of vitamin A may be due either to an intrinsic alteration in the regulatory mechanism of vitamin A storage and metabolism, or to an alteration that is a consequence of vitamin A overdosage. The elevated phosphatase level, which is probably responsible for the bone changes, may be secondary to hepatic damage produced by intake of excess vitamin A. Animal experiments indicate that the toxic effects on bone consist of a speeding up of all normal processes and that decalcification proceeds faster than new bone formation, and we may speculate that the craniotabes present in this case resulted from such a sequence of events. Since craniotabes, no matter what its cause, is confined mainly to a younger group of patients than hitherto reported with hypervitaminosis A, its absence in the reports of previous cases is not strange.

Summary

An unusual case of hypervitaminosis A with severe craniotabes in a 6½ month old infant is presented. This is the youngest infant reported with this condition and the first to present craniotabes.

Symptoms of hypervitaminosis A are compared with those of hypervitaminosis D and with those of infantile cortical hyperostosis. In the case presented prompt and complete disappearance of craniotabes and other symptoms followed withdrawal of administration of vitamin A.

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SPANISH ABSTRACT

Hipervitaminosis A; Reporte de un Caso con Craniotabes Marcado

Se presenta un caso poco comun de hipervitaminosis A con craniotabes severo en un niño de seis y medio meses de edad. Este caso de hipervitaminosis A es el primero reportado en un nino de ésta edad y el primero presentando craniotabes. Los síntomas de hipervitaminosis A son comparables a los hipervitaminosis D y con aquellos de hiperostosis cortical infantil. En el caso presentado, la suspensión de la administración de vitamina A produjo la desaparición rápida y completa del craniotabes y de los otros síntomas.

Duke University School of Medicine

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HYPERVITAMINOSIS A

REPORT OF A CASE IN AN ADULT

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and
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The paucity of published reports of hypervitaminosis A indicates the relatively low incidence of this syndrome. However, the increasing number of publications about the symptom complex since Josephs'[1] article in 1944 suggests that many cases of clinical hypervitaminosis A may have been overlooked in the past. Prompted by new findings, leading medical journals on each side of the Atlantic Ocean recently have had editorials on the subject.[2]

In addition to Josephs' description, Toomey and Morissette,[3] Rothman and Leon,[4] Fried and Grand,[5] Dickey and Bradley,[6] Wyatt, Carabello and Fletcher[7] and Caffey[8] have presented additional material concerning the now well established syndrome of hypervitaminosis A in man. Furthermore, experiments on laboratory animals given large doses of vitamin A have not only helped to delineate the clinical signs but, of greater importance, have provided material for the study of physiological, chemical and histological changes induced by overdosage with this generally comparatively innocuous substance.[9]

As far as we have been able to ascertain, at the time of this publication all the cases presented (eight reported in full and casual reference to eight others) have occurred in young children. Our patient was an adult whose physiological, chemical and general body economy would obviously differ from that of a child or infant. As described below, despite this distinct age differential, the general syndrome in our patient was basically similar to that previously reported in infants and children.

REPORT OF CASE

Mrs. N. R., a 44 year old white woman,[10] was first seen by us on May 25, 1950. While she consulted us chiefly because of excessive loss of hair, it developed that during the preceding six months the patient had been experiencing various difficulties, which included the following: (1) For five months prior to our seeing the patient, her menstrual cycle, though regular, was three days shorter than previously. The flow lasted five days instead of eight and was less than usual. A thorough examination by her gynecologist revealed no abnormalities. (2) Generalized joint and bone pains, migratory in nature, were first present in March 1950. These were treated by thiamine and penicillin injections with equivocal results. The severity of the pains fluctuated a great deal so that at times they would disappear spontaneously; though the discomfort was great, at no time was it necessary for ordinary household duties to be put aside. (3) Examinations performed because of the pains led to the discovery and extraction of two infected teeth. These extractions, performed in March 1950, did not check the joint and bone pains. (4) Soreness and fissuring appeared in January 1950 at the corners of the mouth and the nasal apertures. These also were treated with a series of thiamine injections; there was no apparent improvement. (5) Skin changes which dominated the complaints included generalized pruritus, a dry, rough skin with a widespread branny desquamation and excessive loss of hair beginning in the last two months with thinning of scalp hair and loss of the eyebrows, eyelashes, axillary and pubic hairs and lanugo hairs. (6) She experienced night sweats during the last six months. (7) According to the patient, her eyes were more prominent than they had been previously.

Family History.—The patient's family history was noncontributory. There was no history of skin disease, abnormalities of hair or nails, atopy or other familial disease.

Personal History.—At age 6, the patient had an "eczema" between her fingers. In 1941 an amputation of the cervix was done, and in 1947 the patient had virus pneumonia. Otherwise, the patient has always been a generally healthy person.

Physical Examination.—Abnormal findings included tenderness over various long bones, the spine and the large joints which could be elicited by deep pressure. A slight bilateral exophthalmos was observed which the patient stated had been present for several months; but one must view this observation as being of doubtful significance, for we had not seen the patient prior to the onset of the syndrome. All the other abnormal findings were limited to the skin and its appendages.

The skin was generally warm and dry. The hairs of the scalp, axillary and pubic areas were coarse, brittle, dry and easily pulled from their moorings. Those comprising the eyebrows and eyelashes were almost entirely gone, and no lanugo hairs could be found anywhere on the body. The scalp hair present was difficult to manage and appeared unkempt. A chloasma-like or Riehl's melanosis-like pigmentation was present on each side of the face and neck. A pruritic, excoriated, superficial and finely scaling dermatosis was present over the upper back and all the extremities. Distinct, elevated, minute follicular papules and follicular hyperkeratoses were evident on the extremities and, in particular, on the thighs and lateral surfaces of the arms. Slight scaliness and superficial fissuring were present at the nasal apertures and corners of the mouth. Papular acneform and milia-like lesions were present on the face, particularly on the forehead. The finger nails were soft and brittle, and onychorrhexis was present.

Further questioning at this time revealed that the patient had been taking about 600,000 units of vitamin A daily during the 18 month period prior to our seeing her. This self medication was inspired by a radio "nutrition commentator" who suggested that vitamin A was good for "alleviating dry throats and as a prophylactic for colds." Our patient grasped this cue and, in her zeal, established a daily 600,000 unit dose (supplemented by doses of 1,000,000 units to 2,000,000 units on special occasions, e. g.

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10. Dr. Jacob Cohen of Brooklyn referred the patient to us.

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suspicion of oncoming colds or dry throat). The vitamin preparation employed was supplied in 50,000 unit capsules by a large local pharmacy and contained no vitamin D. The patient's husband somehow began to suspect that this vitamin might be harmful, and the medication was stopped voluntarily on May 20, 1950, five days before we saw the patient for the first time.

Several urinalyses gave results which were normal in every respect, including that for calcium excretion. Basal metabolic

Fig. 1.—Photograph taken June 1, 1950. Note sparseness of scalp hair and unkempt appearance. The scalp may be seen easily through the hair. (Vitamin A self medication started about Dec. 1, 1948 and stopped on May 20, 1950.)

rates determined on two occasions one week before we saw the patient were + 7 and 0; two determined six years ago were — 9 and — 4. Roentgenograms of several long bones and joints were made June 1, 1950 and showed only normal features. Those areas tender on deep pressure were selected for radiography. A scout film of the abdomen revealed no abnormalities such as renal calculi or metastatic calcification.

Therapy and Course.—The only therapy advised was that of continued avoidance of the supplementary vitamin A intake, the patient having ceased to take the vitamin five days before seeing us. Those foods containing large amounts of vitamin A were restricted as much as possible. Though vowing to cooperate, the patient was reluctant to believe that anything as beneficial as a vitamin could actually have caused such difficulties.

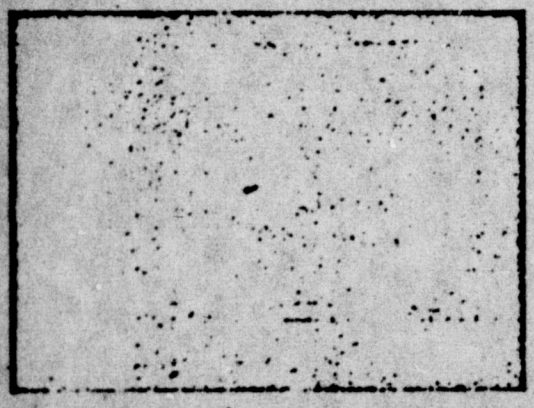

Fig. 2.—Photograph taken June 1, 1950. Note loss of eyebrows and eyelashes. Small milia-like lesions may be seen just above the glabella. Chloasma-like pigmentation is apparent on the lateral aspects of the forehead.

Within 10 days after the patient stopped taking the vitamin A, the joint and bone pains disappeared, as did the pruritus and superficial branny desquamation of the skin. The patient now was convinced of the role of the vitamin in the syndrome. The follicular hyperkeratoses on the extremities and fissuring at the corners of the mouth and nose were gone several days later. Because of the rapidity of involution of these particular lesions, we unfortunately missed the opportunity of getting photographs of them. However, the following photographs, taken on June 1, 1950 (figs. 1, 2 and 3), give various views of the remainder of the syndrome, as evidenced by the pigmentary, hair and skin abnormalities seen on the head; and the photographs, taken on Sept. 26, 1950 (figs. 4, 5 and 6), show the evolution of these changes during the approximately four month abstinence from vitamin A medication.

As the latter half of June approached (four weeks after the cessation of additional vitamin A consumption), new, fine and coarse hairs began to appear in all areas where previously they had been lost. However, the finger nails continued to become worse, and it was only at the end of July (10 weeks after the vitamin A capsules had been discarded) that they began to show a tendency to revert toward normal. Though the dystrophy and recovery of the nails did lag behind that of the other epidermal appendages, when seen in September (about four months after the original visit) the patient was normal except for the shortness of the hair and the residual chloasma-like pigmentation (figs. 4, 5 and 6).

Fig. 3.—Photograph taken June 1, 1950. Chloasma-like pigmentation is easily seen, as is the lack of eyebrows, eyelashes and facial hair. Milia-like lesions are present on the cheek.

The night sweats disappeared, and sweating was reported to be normal throughout the summer.

The hair gradually became more manageable, and its fall became minimal by mid July. The menstrual cycle returned to what it had been one year previously and to the normal intervals which had always existed prior to that time. Little or no change occurred in the slight exophthalmos. At no time did the patient experience difficulty with her eyesight, though she did claim that her eyelids had a "granular feeling" shortly before she came to the office.

COMMENT

Although the picture of hypervitaminosis A is not yet generally well known to clinicians, there are sufficient reports and experimental data for one to consider it a well established and characteristic syndrome. Its inclusion for the first time in standard American medical text-

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books [11] will doubtless lead to a more general recognition of this symptom complex by the practitioner.

As far as we have been able to discover, up to the present all articles on the undesirable effects of excessive amounts of vitamin A have dealt with the syndrome as occurring in very young children and laboratory animals. To the best of our knowledge the present report is the first to record observations of hypervitaminosis A in the adult human being. The findings closely follow the pattern already established in children and experimental animals, but several deviations from and additions to the accepted syndrome were present in this case.

Menses.—As all the previously reported cases occurred in infants, the menstrual changes in our patient automatically introduce another and new aspect of prolonged vitamin A overdosage. One cannot rule out the possibility that the menstrual changes in our patient may have been a spontaneous or physiological alteration since the patient was in the age group of those often undergoing menopausal changes. Nevertheless, the onset of the menstrual disturbances at the time of the other disturbances and the reversion to normal menses when the vitamin A medication was stopped speak strongly in favor of the assumption that the alterations in menstruation were actually a part of the hypervitaminosis A syndrome. If this assumption is correct, then either endocrine imbalance or disturbances in bleeding or coagulation might, one or both, underlie the menstrual aberrations; the few studies done on our patient shed no light on the cause of the menstrual changes.

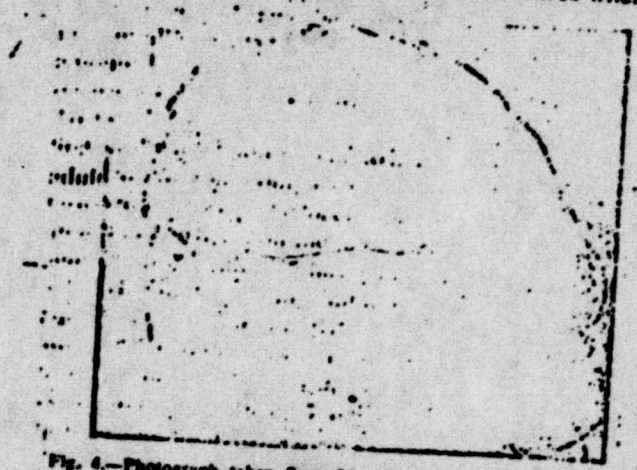

Fig. 4.—Photograph taken Sept. 26, 1950. Note regrowth and orderly appearance of the scalp hair. Short hairs extend over the upper part of the forehead. Note the return of the facial, eyelash and eyebrow hair.

In this connection it is noteworthy that in other cases of hypervitaminosis A, hypoprothrombinemia, correctable by vitamin K administration, has been shown to be the basis for hemorrhages (for example, such as that which followed tonsillectomy in Josephs' patient [1]). Severe hemorrhage and even death have occurred spontaneously and after minor trauma in animals with hypervitaminosis.[12] Therefore, in any suspected or proved case of hypervitaminosis A, caution should be exercised in regard to interferences that might cause bleeding. Even minor surgical procedures may precipitate severe hemorrhage—though this fortunately did not occur after dental extractions in our patient.

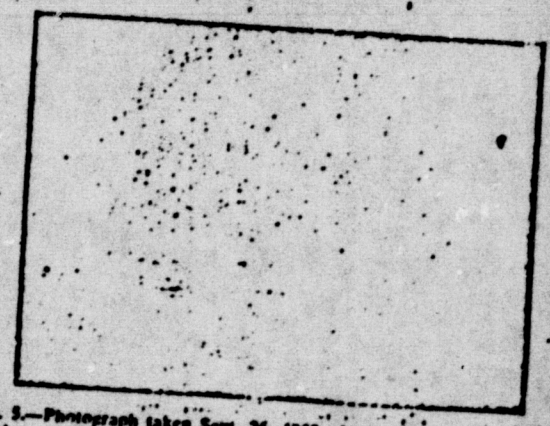

Fig. 5.—Photograph taken Sept. 26, 1950. Note excellent hair regrowth in eyebrow and eyelash areas, as well as on the face. Chloasma-like pigmentation may still be seen on the forehead. Milia-like lesions are gone.

Although the mechanism of vitamin A hypoprothrombinemia is unknown, it appears possible that the excess of vitamin A may perhaps interfere with the synthesis of vitamin K by the intestinal flora, or it may disturb absorption or increase the need for vitamin K, or it may destroy

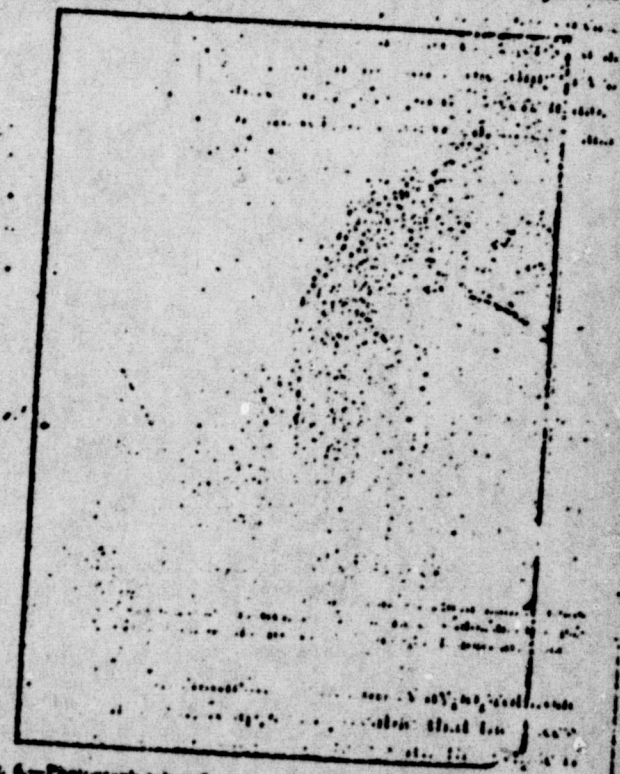

Fig. 6.—Photograph taken Sept. 26, 1950. Note extensive hair growth on the face and regrowth in the eyebrow and eyelash areas. The chloasma-like pigmentation, though lighter, is still visible. Milia-like lesions on the cheek are gone.

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The fractures observed in the animal with vitamin A toxicosis are not prevented by vitamin K which, however, corrects the ever present hypoprothrombinemia. These two manifestations may also be isolated from one another by the administration of bishydroxycoumarin (dicumarol®) which causes hemorrhage but not fractures.[13]

Pigmentation.—Not heretofore described as a component of this syndrome was the chloasma or Riehl's melanosis-like pigmentation present in our patient. Again, one could speculate about the appearance of this pigmentation being a coincidence instead of a result of the excessive vitamin A intake. Yet its concomitant appearance with the other well established signs and symptoms and its fading on withdrawal of the vitamin A (though during this three month period the patient was exposed regularly to the summer sun) lead us to incline to the opinion that this is a newly observed component of hypervitaminosis A. Our meager understanding of the basic physiological mechanisms underlying the appearance of chloasma or Riehl's melanosis makes it impossible for us to explain this phenomenon.

Skeletal System.—Apparently the mature structure of bone is not so labile as a child's in its response to outside influences. This could well explain why the roentgenologic features regularly and characteristically found in children were missing in our adult case. Wolbach and others make the following statement in connection with their extensive studies in laboratory animals: "It should be kept in mind that the results on bone of excessive vitamin A administration are exhibited only in the growing animal and only in regions undergoing growth."[9a] Moore and Wang noted the same findings and wrote: "In adult rats, the bones are probably more resistant to fractures, since we detected no breakages in our older animals."[9d]

Itching.—Generalized pruritus is another feature which has been a constant component of the syndrome. Infants and animals fed excessive doses of vitamin A have regularly shown the presence of itching. Generalized moderately severe itching was also a prominent symptom in our patient. The questions of the origin and mechanism of this pruritus are still unsolved.

Is the pruritus due to primary epidermal changes? Could the threshold be lowered locally by the faulty keratinization and dryness of the skin? This would be the simplest and, therefore, the first hypothesis for investigation. However, hypervitaminosis A produces many other complex systemic and internal changes which can lead to itching. These include alterations in the delicate balance and interplay between the liver and the nervous, cardiovascular and endocrine systems; local and general alterations in physical and chemical balance, as exemplified by the ratio of anions, cations and colloidal particles; changes in pH and surface tension, disturbances in enzyme systems—all or any of these may directly or indirectly influence both peripheral and central prurigenic irritability. All these factors must, therefore, be considered in the further study of this complex problem.

Keratin Structures.—To dermatologists and to all [illegible] must attach to the changes found in the horny structures, the hair, finger nails and horny layers of the skin. In our case also, all these structures were disturbed by the inordinate consumption of vitamin A and in a manner remarkably reminiscent of hypovitaminosis A.[14] Previous reports have referred to these features in hypervitaminosis A, but no correlation has been made with normal morphologic changes in the epidermis and its appendages or with known physiological functions of the skin.

Eye Symptoms.—For the sake of completeness, it must be mentioned that exophthalmos, though in our case of questionable connection with the hypervitaminosis, has been a feature seen by several investigators in laboratory animals receiving high doses of vitamin A.[15] (Also excess vitamin A has been said to have no effect on dark adaption.[16])

Results of Blood Studies *

	May 10	May 28	June 1	June 14	Sept. 28
Red blood cells	..	..	4,200,000	..	..
White blood cells	12,000	..	7,400	..	6,500
Hemoglobin, Gm.	..	..	14	..	..
Polymorphonuclear leukocytes, %	48	..	65	..	64
Lymphocytes, %	21	..	24	..	29
Monocytes, %	11	..	11	..	7
Total calcium †	..	..	9.2	..	..
Inorganic phosphate †	..	..	3.5	..	..
Alkaline phosphatase, Bodansky units per 100 cc.	..	4.0	..	..	..
Cholesterol †	..	205	..	205	215
Cholesterol esters †	..	120 or 59%	..	..	....
Proteins, total, Gm./100 cc.	..	7.7	..	..	..
Albumin, Gm.	..	5.0	..	..	....
Globulin, Gm.	..	2.7	..	..	..
Albumin-Globulin ratio	..	1.8	..	..	.. ..
Total carotenoids, units per 100 cc.	..	62.5	..	96.0	115
Vitamin A, blue units per 100 cc. ‡	..	60.0	..	62.0	30.0
Lipids, total † §	..	..	..	800	770
Fatty acids †	..	..	..	605	560
Lipid phosphorus †	..	..	..	14.2	10.0

* Dr. M. Reuter of the University Hospital of New York University-Bellevue Medical Center supervised the chemical examination of blood specimens, and Drs. Jacob Cohen and Jacob J. Kelly of Brooklyn furnished other information about the patient.

† Milligrams per 100 cc.

‡ Price-Jones method used.

§ Bloor method used.

Laboratory Studies.—As in previous investigations in infants and laboratory animals with hypervitaminosis A, few detectable changes in the blood picture were present in our patient (table). On the other hand, in contrast to some of the previous reports, Mrs. N. R. had no abnormalities in alkaline phosphatase and mineral metabolism in blood or urine studies done several days after the vitamin A ingestion was stopped. The total plasma proteins, red blood cells and hemoglobin, repeatedly re-

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ported as below normal in some of the children with this syndrome, were normal in this instance.

Several abnormalities were present in our patient: the white blood cells were increased in number (13,000 per cubic millimeter) on the initial study and subsequently receded to normal figures (7,400 and 6,500), which were similar to counts done on the patient over a number of years. An increment in monocytes was noted on three separate occasions, a decrease being noted on the last count.

As found by all other investigators, the vitamin A level was much higher than normal. When the supplementary vitamin A intake was stopped, within a four month period a definite recession toward accepted normal figures occurred. During the period when no supplemental vitamin A was being taken, the total carotenoids rose to a figure slightly above normal. Concomitantly, the originally elevated total lipids, lipid phosphorous and fatty acids fractions reverted toward standard figures. It may be worthy of particular note that the cholesterol levels remained within the normal range throughout.

All other blood studies and urinalyses gave normal findings in every respect. The fact that no history or no evidence of renal disease was elicited indicates the probable lack of relation between the mechanisms in our case and the interesting observation of Popper and his associates [17] who found that "hypervitaminosis A judged by plasma levels was found in disease of the nephritic type." Apparently, even in the absence of liver damage, the destruction of the kidney parenchyma either causes retention of a protective substance or decreases the production of a substance destructive for vitamin A. Therefore, feeding of excessive vitamin A produces a much higher vitamin A blood level in persons with nephritis than in normals. Whatever the mechanism, it is certain that "endogenous hypervitaminemia A" (i. e., without apparent excessive intake) does occur and must be kept in mind in the presence of isolated reports of blood abnormality.[18] The history of excessive vitamin A intake, variations in the vitamin A tolerance curve, knowledge of the patient's general physical condition and the height of the blood vitamin A levels usually permit the ready differentiation between endogenous and exogenous hypervitaminemia A. In our patient, the evidence points unequivocally to the exogenous form.

Other Features of Hypervitaminosis A.—Several aspects of hypervitaminosis A previously described in infants and children were absent in the present case. These additional components were hepatomegaly, splenomegaly, hypochromic anemia, depressed serum proteins, elevated alkaline phosphatase, clubbing of fingers and an abnormal appetite for butter and fish liver oils. It is very likely the variations in response of human beings to an overdosage of the same vitamin are dependent on such factors as the amount, the length of time and how often the medication is taken. The different physiological and biochemical demands and stresses in each person and in each age group, and even in each organ or structure within an organ, doubtless play important roles in vitamin A metabolism and in the determination of the pictures produced by excess or deficiency of intake.

Many other factors must influence the blood levels and the susceptibility of a person to be overwhelmed by vitamin A. One of these factors is the form or preparation in which the vitamin is taken or administered (in food or a supplement); some available preparations are oils, others acetates or alcohols, while still others have emulsifying agents added.[19] The status of the gastrointestinal tract, including its enzymes, flora and physical and chemical emulsifying capacity, as well as the status of the intestinal wall, and the transport system, including the ability of the chylous fluid and blood to carry the vitamin, are other factors. The status of the liver, thyroid, kidney and other internal organs and the interrelationship between them and vitamin A would also be important. Different periods of growth, bodily stress and development obviously vary the need for the vitamin. The storage areas, primarily the liver, and the ability or inability to store or release the vitamin [20] should also be considered. The form of the vitamin, whether an alcohol or not, has a great deal to do with this.[19a] The destruction, excretion and conversion of the vitamin, and the states, functions and needs of the organs of response, of the "target structures" at the time the vitamin is exhibited (for example, the state and needs of the individual hair follicle at the moment; the momentary rate and form of activity of the sebaceous glands; the quiescence or activity of bone growth) are other influencing factors.

Vitamin A Therapy.—It is not the purpose of this paper to review all the indications for vitamin A therapy. However, large doses, 100,000 to 500,000 international units daily, taken for varying or even indefinite periods of time, are being advocated for the treatment of many conditions.[21] Of significance in this regard is that the advocated therapy sometimes has little clinical or experimental justification.

In view of the present widespread use of extremely large doses of vitamin A, it is remarkable that scarcely a reference has been made to clinical signs of "toxic" hypervitaminosis A occurring in patients receiving large doses for relatively long periods of time. Fortunately, in most patients the zone between adequate prophylactic and therapeutic doses and the toxic doses appears to be very wide. Nevertheless, the present case again emphasizes that the physician administering large doses of vitamin A must be on the lookout for signs and symptoms of toxicity and should have regular blood examinations for vitamin A levels performed on all patients on high doses for periods of more than a few weeks.

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roid function plays the role of a common factor is also as yet unelucidated.

The possibility of therapy with thyroxin was considered in our patient but discarded because of conflicting reports as to its efficacy.[23] One group has even stated that the symptoms of hypervitaminosis A in laboratory animals were enhanced by administration of thyroid.[23b] Since apparent spontaneous recovery occurs from the toxic manifestations of hypervitaminosis A, no active therapy was instituted in our case. As was to be expected, the result of the cessation of the excessive vitamin A intake was a satisfactorily prompt and complete disappearance of the signs and symptoms.

SUMMARY

The observations and course of a case of hypervitaminosis A, apparently the first to be reported in an adult, are presented. Several possible features of the syndrome not observable in infants or children are described in the adult (e. g., menstrual changes, absence of radiologic changes of the bones, chloasma or Riehl's melanosis-like pigmentation). The effects and mechanisms of excessive vitamin A on various organs and systems and, in particular, on the structures of the skin are discussed. The resemblances between the changes of hypervitaminosis A, hypovitaminosis or avitaminosis A and hypothyroidism are described, and some thoughts on the possible interrelations are submitted.

999 Fifth Avenue (Dr. Sulzberger).

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Hippocratic Oath.—The modernisation of the Hippocratic Oath by the World Medical Association, known as the Declaration of Geneva (1948), is known to very few and is worthy of note. It runs:—

Now being admitted to the profession of Medicine, I solemnly pledge to consecrate my life to the service of humanity. I will give respect and gratitude to my deserving teachers. I will practice medicine with conscience and dignity. The health and life of my patients will be my first consideration. I will hold in confidence all that my patient confides in me. I will maintain the honour and noble traditions of the medical profession. My colleagues will be as my brothers. I will not permit consideration of race, religion, nationality, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect of human life, from its conception. Even under threat I will not use my knowledge contrary to the laws of [illegible] and, upon my honour.

Otro caso de hidrocefalia aguda benigna del lactante después de una dosis masiva de vitamina A

Por el Dr. Jose M.ª Cluet García
Barcelona

En la sesión del 20 de febrero del corriente año de 1951 de la Sociedad de Pediatría de Paris, y publicada en el número 5 de *Archives Francaises de Pédiatrie*, [illegible]

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Otro caso de hidrocefalia aguda benigna del lactante después de una dosis masiva de vitamina A

Por el Dr. Jose M.ª Cluet García
Barcelona

En la sesión del 20 de febrero del corriente año de 1951 de la Sociedad de Pediatría de Paris, y publicada en el número 5 de *Archives Françoises de Pédiatrie*, JULIAN MARIE y JORGE SÉE presentaron en una comunicación tres casos de lactantes de tres a siete meses, quienes sufrieron, de las doce a las catorce horas después de una ingestión masiva de vitaminas A y D, y hallándose en plena salud, una distensión considerable de la fontanela de comienzo brusco y vómitos repetidos, con ausencia de fiebre y de signos meningeos.

Después de varias discriminaciones, eliminaron a la vitamina D como causante de este cuadro, achacándolo a la vitamina A y diferenciándolo de la intoxicación crónica producida por ella por sus distintos síntomas (anorexia, irritabilidad, algias en pies y manos e irregularidades en los huesos largos), así como también por la distinta forma de absorción. Dosis regulares y repetidas, en un síndrome; dosis única y masiva, en el otro.

En los tres casos practicaron la punción lumbar, que proporcionó un líquido normal.

Al leer estos casos y su comentario, recordamos inmediatamente otro vivido por nosotros hace muchos años, y, si bien le dimos la importancia debida, ya que desde entonces somos muy cautos en los choques de vitamina A en los lactantes, no lo publicamos, por tratarse de un caso aislado y quedar sorprendidos con el mismo, no sabiendo qué explicación darle, como confiesan haberles sucedido también los autores franceses en el primero que observaron.

En resumen, se trataba de una niña de tres meses, a la que habíamos recetado dosis masivas de vitaminas A y D, pero por separado, en dos distintos envases, injiriendo solamente su frasco de la primera el 26 de marzo de 1936, por la mañana, en ayunas. Por la tarde presentó mareo, náuseas y vómitos; apirética. Llamados urgentemente, acudimos a última hora de la tarde, y encontramos a la niña con aspecto normal, pero su fontanela tensa y algo abombada, sin signos de Kernig ni de Brudzinski, sin contrac-

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Resfriados	Tabletas de Penicilina «*Leti-Uquifa*» Vacuna Anticatarral «*Leti*» Asmobacterial «*Leti*» Rinocillin «*Leti-Uquifa*» Chiclés de Penicilina «*Leti-Uquifa*» Perlaminas A masivas «*Leti*»
Enfermedades Reumáticas	Vacuna Antirreumática «*Leti*» Equimorfin «*Uquifa*» Equipón «*Uquifa*» Perlaminas «*Leti*» (A + D, A masivas, D masivas y D supermasivas)
Enfermedades de infancia	Anatoxina Diftérica «*Leti*» Vacuna Anticoqueluchosa «*Leti*» (preventiva y curativa) Perlaminas «*Leti*» Metabasal Líquido «*Leti*»

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Codeinfós «Uquifa»
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Resfriados
Tabletas de Penicilina «Leti-Uquifa»
Vacuna Anticatarral «Leti»
Asmobacterial «Leti»
Rinocillin «Leti-Uquifa»
Chiclés de Penicilina «Leti-Uquifa»
Perlaminas A masivas «Leti»

Enfermedades Reumáticas
Vacuna Antirreumática «Leti»
Equimorfin «Uquifa»
Equipón «Uquifa»
Perlaminas «Leti» (A + D, A masivas, D masivas y D supermasivas)

Enfermedades de infancia
Anatoxina Diftérica «Leti»
Vacuna Anticoqueluchosa «Leti» (preventiva y curativa)
Perlaminas «Leti»
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Tabletas de 5 mg. Ampollas de 5 mg.
"Fuerte" Ampollas de 25 mg.
"Fortísimo" Ampollas de 100 mg.

E. Merck

tura de nuca y con pupilas normales. Al día siguiente continuaba apirética, habiendo cedido los vómitos; en cambio, la fontanela había aumentado su tensión de una manera exagerada, "con tendencia a la separación de los parietales". Y continuaba la ausencia de los signos meningeos.

No se hizo la punción por reparo de los padres, ante la apirexia y buen estado general. Al día siguiente, cuando nos presentamos dispuestos a hacerla, nos encontramos con que la fontanela estaba deprimida y la niña completamente normal.

Este caso nuestro parece copiado de los de MARIE y SÉE en todos los detalles: ingestión de la dosis masiva de vitamina A (y con ello se alejan todas las dudas sobre la vitamina causante del cuadro), y a las pocas horas, presentación de vómitos y tensión de la fontanela, que va en aumento hasta adquirir caracteres exagerados, para, a las cuarenta y ocho horas del accidente, desaparecer rápidamente, convirtiéndose en una depresión marcada, de un modo espontáneo y sin precisar la punción lumbar. Entre los síntomas negativos figuraban la falta de fiebre y de los signos de irritación meníngea.

Terminan los autores franceses su comunicación no sabiendo cómo explicarse la causa de esta hidrocefalia aguda, suponiéndola debida a una hipersecreción de líquido céfalorraquídeo, a defecto de reabsorción del mismo o a modificación de su presión de origen vasomotriz o nervioso.

Recalquemos, como ellos, que este accidente, indudablemente provocado por la ingestión de vitamina A a dosis masivas, es de curso benigno; por tanto, no contradice su uso terapéutico en casos necesarios, pero a dosis más razonables.

RESUMEN

Se presenta un caso de hidrocefalia aguda benigna, después de un choque vitamínico A, sin fácil explicación de su mecanismo patogénico, sin signos meningeos y con buen pronóstico.

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Milk is a good source of riboflavin, nicotinic acid, and vitamin E. Neither mother's nor cow's milk is a good source of vitamin K. Vitamin F, consisting probably of some nonsaturated fatty acids, is present in the cream.

GLASER, Jerusalem.

OSTEOSCLEROTIC SYNDROME AND OVERDOSAGE OF VITAMINS A AND D. G. FRONTALI, Schweiz. med. Wchnschr. 82:430 (April 12) 1952.

A 4-year-old girl was treated with streptomycin for miliary tuberculosis of the lungs. In addition, she received 60,000 I. U. of vitamin A and 40,000 of vitamin D per day. She was dismissed after four months. The miliary lesion had cleared, as well as evidence of renal involvement. At home vitamin A medication was continued with a dosage of 150,000 I. U. every second day. About two months later the patient was readmitted. Widespread osteosclerosis, including the cranium, particularly the base, was found. There were retention of nitrogen in the blood, elevation of the blood pressure, hypoisosthenuria, anemia with reduction of erythropoietic activity, and possibly some hepatic lesions. These lesions did not regress as rapidly as the osseous hypercalcification, which on cessation of vitamin A medication disappeared nearly entirely.

AMBERG, Rochester, Minn.

THE ABSORPTION OF VITAMIN A BY RECTUM. LUIGI BARILLA and PIERFRANCESCO PERUZZI, Riv. clin. pediat. 50:196 (March) 1952.

The authors report the vitamin A blood levels obtained in 10 children from 11 months to 10 years of age after vitamin A has been introduced by rectum. The authors consider this method very useful, having found a quick absorption and therapeutically sufficient drug levels.

FROM THE AUTHORS' SUMMARY.

ANOTHER CASE OF ACUTE BENIGN HYDROCEPHALUS IN AN INFANT AFTER A MASSIVE DOSE OF VITAMIN A. JOSE M. CLUET GARCIA, Acta pediat. españ. 9:1448 (Dec.) 1951.

The author presents a case of a 3½-month-old child who had the history of ingestion of a massive dose of vitamin A. The child had the usual symptoms of hypervitaminosis A plus meningism, with positive Kernig and Brudzinski reflexes, but without fever. The fontanel was bulging, and there was obvious parietal suture separation. The child recovered without spinal puncture or other treatment and with no apparent sequelae.

The theory is that the hydrocephalus is due to hypersecretion of cerebrospinal fluid, to a defect in the mechanism for reabsorption of this fluid, or to a modification of the fluid pressure of vasomotor or nervous origin.

ALLEN, San Francisco.

Hygiene; Growth and Nutrition; Public Health

EPIDEMIOLOGY OF CHILDREN OF SCHOOL AGE. MEGIAS VELASCO, Acta pediat. españ. 10:83 (Jan.) 1952.

The author reports the defects found in the examination of 10,800 school children. Various defects, such as tonsillitis, cardiac defects, and defects of eyes and ears, are reported, but most of the study is devoted to the number and stage of the cases of tuberculosis discovered.

ALLEN, San Francisco.

THE IMPORTANCE OF SOCIAL FACTORS IN THE ETIOLOGY OF DYSTROPHY IN THE INFANT. MARIA L. SALDUN DE RODRIGUEZ and JOSE M. PORTILLO, Arch. pediat. Uruguay 23:89 (Feb.) 1952.

Etiological factors of infantile dystrophy are connected with social conditions [illegible]

Purely medical care has little effect on the cure and prevention in the group. The basic factors already mentioned must also be should be trained so that they will be able to make an exact socia use of community resources, or simply train the mother and the

Basic knowledge of child rearing and hygiene should be disse treatment and prevention of dystrophy. Well baby clinics a founded or expanded; sufficient and correct nutrition should be as care in case of illness, and, especially, there is great need of qua

FROM TH

INCREASE (NOT DECREASE) OF MORTALITY IN VIENNA IN THE THE YEARS 1948 TO 1951. HERBERT ORAL, Wien. klin. Wchn

The author noted that the mortality of infants in the third mo decrease, compared with that of the second month, as in Austria a remained the same, or increased. This is brought into relation w away from home by the mothers.

AU

Prematurity and Congenital Deform

CONGENITAL CATARACT AND MENTAL DEBILITY. M. SCHACHTE 1950.

Five cases of congenital cataract and mental debility are descri history of mental deficiency was obtained, the condition being hereditary factors. The third case history revealed rubeola of th months of pregnancy; in one case the mother was syphilitic, and hereditary nor exogenous factors could be elicited except prematu

SOME ASPECTS OF PREMATURITY. F. CANIVELL and M. ZAMORA, 1951.

The author points out that, although infant mortality rates have the respiratory and gastrointestinal diseases because of better nutrition sanitary conditions, the deaths due to prematurity have not fallen in

The rate of deaths due to prematurity, however, fell 50% in cent care of the premature as compared with a 21% fall in general hosp These figures were taken for the decade from 1936 to 1946.

The statistics in other countries are also cited. Spain stands b great decrease in mortality due to prematurity and those with poor need for premature centers.

There is also need for better reporting because, although Spain l per thousand live births, it has a high mortality rate in prematu socioeconomic groups.

The following topics concerned with prematurity are discussed: measures; (2) factors during gestation; (3) traumatic factors at birth (5) injury to the respiratory center, and (6) the anoxia due to these fa ment of the lung tissue in premature infants.

Treatment is outlined for various conditions causing death due

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U.S. Child. 94:679, 1952

J.A.M.A.
Vol. 146, No. 17: 1573-4, 1951

CHRONIC VITAMIN A POISONING

REPORT OF A CASE

George Bair, M.D., New York

Hypervitaminosis A is a syndrome first described by Josephs in 1944.[1] Subsequently, there have been 13 additional cases reported.[2] Observers have noted the following characteristic manifestations of the entity: external cortical thickenings of the affected bones, pain and swelling over the long bones, irritability and fretfulness, and increased vitamin A concentration in the blood.

REPORT OF CASE

B. Z., a 28-month-old white child, was first seen by me on April 15, 1950, after he had been ill at home for two and one-half weeks. His main complaints were painful swellings of the left foot, right forearm, and temporal regions. He also complained of severe itching of the back and arms. At the onset, although limping, the child was able to get around, but within a few days the pain became so severe that he refused even to attempt to walk. Penicillin and aureomycin were administered during the first two days of the illness, but were discontinued because he became progressively worse.

Past History.—The child had been a full-term, normal-delivery infant weighing 6 lb. 7 oz. (2.9 kg.) at birth. Five days

Fig. 1.—Left foot, showing swelling in region of fifth metatarsal.

post partum his mother died of virus pneumonia, so that he was brought up by grandparents. His feeding history was unusual in several respects. Since he rejected solids for the most part, his food was taken strained or mashed. He craved butter and ate large quantities of it. In addition, he showed a preference for milk, cheese, eggs, liver, carrots, tomatoes, and sweet potatoes. His appetite had been good until the onset of symptoms, after which he rejected all food. The vitamin intake was supposed to be 20 drops of percomorph liver oil daily. However, when the diagnosis became evident, questioning disclosed that because of an error a considerably larger amount of oil had been given.

Seven weeks before the onset of symptoms, the child complained of itching in the back of his neck. During the following weeks the pruritus became more intense and spread down the back and arms. This was so troublesome that a doctor who was consulted thought it was an allergic condition.

Physical Examination.—Examination revealed a well-developed, well-nourished boy who appeared sick and in pain. The child seemed to have a stiff neck when sitting up. He was fretful and irritable. His face was puffy; the lips, in contrast, were dry and fissured. Thin serous fluid ran from the nose. Bilateral temporal swellings, larger on the left, were visible and palpable. A fusiform swelling covered the fifth left metatarsal. The dorsa of both feet were edematous, and the right forearm was swollen.

All swellings were hard and tender. Only one area, the outer aspect of the fifth left metatarsal, was hot and bluish in color. The entire body, even those parts which were not swollen, was tender to the touch.

The tonsils were enlarged.

There was no palpable enlargement of spleen or liver. No abnormal masses were felt in the abdomen.

At no time during the illness did the temperature rise over 100 F.

Hemoglobin value was 79%; the red blood cell count was 4,900,000; the white blood cell count was 10,200; platelets 240,000; neutrophils: nonsegmented 6%, segmented 39%; eosinophils 2%, lymphocytes 45%, monocytes 7%, plasma cells 1%; hematocrit reading was 35.3; icterus index, two units; sedimentation rate (Westergren), 56 mm. in one hour (normal is up to 15 mm. in one hour). The findings in the urine were normal.

Blood vitamin A level on April 18, 1950, was 1040 I. U. (normal 50-150 I. U.).

Fig. 2.—Right ulna, showing cortical thickening in the middle third of the shaft.

X-ray examination completed on April 15, 1950, revealed the following abnormalities:

Left Radius: Normal except for slight swelling of the soft tissues adjacent to the distal lateral aspect of the shaft.

Right Ulna: Smooth, homogenous, moderately dense external cortical thickening in the middle third of the shaft. The margins of this hyperostosis were smooth and merged imperceptibly with the marginal cortex. There was no evidence of destruction. Distinct soft tissue swelling was seen contiguous to the cortical thickening.

Dr. John Caffey assisted in the preparation of this paper.

Department of Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals.

1. Josephs, H. W.: Hypervitaminosis A and Carcinomata, Am. J. Dis. Child. 67:33 (Jan.) 1944.

2. Toomey, J. A., and Mermagetto, R. A.: Hypervitaminosis A, Am. J. Dis. Child. 73:473 (April) 1947. Rothman, P. E., and Loon, E. E.: Hypervitaminosis A, Radiology 51:368, 1948. Dickey, L. B., and Bradley, E. J.: Hypervitaminosis A: Case Report, Stanford M. Bull. 6:343, 1948. Fried, C. T., and Grand, M. J. H.: Hypervitaminosis A, Am. J. Dis. Child. 79:473 (March) 1950. Caffey, J.: Chronic Poisoning Due to Excess of Vitamin A, Pediatrics 5:672, 1950.

Right Femur: Faint cortical thickening along the medial aspect of the middle third.

Right Fibula: Slight hyperostosis in the midshaft laterally.

Left Tibia: Cortical hyperostosis along the lateral and anterior aspects of the proximal end of the shaft. Adjacent soft tissue was swollen.

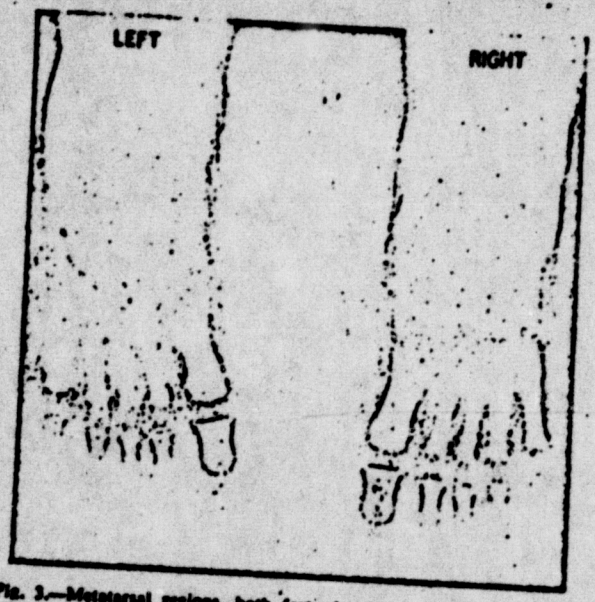

Fig. 3.—Metatarsal regions, both feet, showing lesions and soft tissue swelling over left fifth metatarsal.

Left Fifth Metatarsal: Moderately extensive cortical hyperostosis along the entire shaft. Considerable soft tissue swelling was present in this region.

New bone formation was also seen in the left third and fourth metatarsals and fourth right metatarsal.

Skull: Distinct periosteal new bone formation, less dense than the bones of calvarium, homogenous in character, and similar to hyperostosis present in the long bones. The largest patch of cranial hyperostosis was on the undersurface of the occipital bone extending to and on the left side of the foramen magnum. Smaller, more discrete areas of denser hyperostosis were present in each temporal region, and were more marked on the left side.

Fig. 4.—Skull, showing large patch of hyperostosis on undersurface of occipital bone.

Subsequent Course.—All vitamin supplements and excessive amounts of butter were eliminated from the diet. Within three days the child was able to walk, even though the metatarsal swelling had become more pronounced. The child appeared happy and seemed to be greatly improved. One month later, the metatarsal swelling was practically gone. The swellings of the forehead were still present, but were no longer painful or tender. In roentgen films made at the same time, all the hyperostoses except those in the skull had disappeared. Blood vitamin A level was 750 I. U.

COMMENT

Through a misunderstanding on the part of the grandmother, a teaspoonful of percomorph liver oil was given instead of 20 drops. Thus the child received in excess of 4 gm., or 240,000 units, of vitamin A daily during a period of at least three months. Prolonged continuous administration seems to be necessary before symptoms appear in children. Because of this, the administration for long periods of large doses of vitamin A in the treatment of skin diseases would seem to be a potentially dangerous procedure.

Although 14 cases have been reported, only two others showed swelling in the head. Neither of these cases showed as marked periosteal involvement as the one described above. The location of new bone formation on the undersurface of the occipital bone has never been reported previously. After one month, x-ray of the skull still revealed marked hypertostosis. Apparently new bone formation in this area persists longer than in other affected bones. Bony proliferation and high vitamin A levels were present for some time after the patient was otherwise normal.

Fig. 5.—Skull, showing bilateral temporal hyperostoses.

SUMMARY

A case of hypervitaminosis A with the typical findings and an unusual cranial bone involvement is presented.

Because of the dangers of overdosage, caution is advised in the administration of vitamin A as a standard procedure in the feeding of healthy infants.

The prognosis in recognized cases is excellent after stoppage of excess vitamin A.

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Leidem (hohe Konzentration an Gold oder an Cyan) und bei langen Zusammenwirken kann der Cyan-Zusatz die Wirkung des Goldes verstärken. Dies wird zurückgeführt auf die Bildung eines Methämoglobin-Gold-Cyan-Komplexes, der die kolloid-osmotische Hämolyse hemmt.

Quantitativer Vergleich der verschiedenen Komplexbildner zeigt vor allem die große Ueberlegenheit des BAL in Uebereinstimmung mit den Erfahrungen der Therapie.

Auch die Hemmung läßt sich durch Komplexbildner rückgängig machen, und zwar im Gegensatz zu den Verhältnissen bei der kolloid-osmotischen Hämolyse, unabhängig vom Zeitintervall zwischen Goldsole-Zusatz und Komplexbildner-Zusatz. Darin wird ein weiterer Hinweis auf die Verschiedenartigkeit der Angriffspunkte für die beiden Effekte gesehen. Auch hier steht BAL in bezug auf die molare Wirksamkeit an der Spitze der geprüften Komplexbildner.

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(Clinique Pédiatrique de l'Université de Rome – Directeur: Prof. G. Frontali)

Syndrome ostéosclérotique

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Le surdosage de vitamines liposolubles est signalé avec netteté croissante. A l'étude expérimentale et clinique de celles-ci ont contribué mes collaborateurs *Porto, Malaguzzi*, Cremisini, à côté de nombreux auteurs étrangers.

Entre autres se distingue pour sa singularité un cas qui a donné des considérations théoriques et pratiques d'une certaine [illegible].

L'enfant [illegible] d'août, E. A. M., F., de 4 ans, a été accueillie à l'[illegible] le premier fois en avril 1949 à l'âge de 10 mois, présentant [illegible] une fièvre avec maximum le soir jusqu'à 38-39° et [illegible].

Le poids à cette première entrée, était de 6,1 kg (comme à la station de 67 cm (comme à 7 mois). Elle présentait les signes [illegible] D'Espine et une modeste hépato-splénomégalie.

L'administration de Monbar (1:1000) était formellement [illegible].

L'épreuve tuberculinique révélait en dehors d'une adénopathie [illegible] une réaction [illegible] assez diffuse.

Le [illegible] contenait un liquide [illegible] normal, sans [illegible].

Les urines d'entrée donnaient: présence d'albumine à [illegible] de sédiment des cylindres hyalins-granuleux.

Le diagnostic était de tuberculose miliaire aiguë, le streptomycine [illegible] 1 gr. par jour, par voie intramusculaire.

A cette époque nous ajoutions des huiles [illegible] à la vitamine A (10 gouttes d'Axeril = 50 000 U.I.) et la vitamine D (Abtelin 500, 1 ampoule chaque 20 jours).

Pendant ce traitement nous avons assisté à un net [illegible] de la maladie pulmonaire, avec l'exception de quelques [illegible] pulmonaire. En attendant le foie et [illegible] aux limites normales. Les urines se sont normalisées. L'albumine s'est réduite à 0,25 gr.

En même temps apparaissait et s'aggravait une anémie hypochrome [illegible] 2 millions, Hb. 42%, index globulaire [illegible], sérum-[illegible] 37%, osmot. [illegible], leucocytes 37%, [illegible].

[illegible] une activité érythropoïétique [illegible] de la série rouge et un quotient [illegible].

[illegible] 1%, myélocytes 4%, [illegible] 1%, polynucléaires 22%, [illegible] 12%, lymphocytes 37%, [illegible] 2%, polychromatophiles 12%, orthochromes 10%, [illegible] 1%, [illegible].

Mon assistant, le Dr *Malfanti*, était chargé par moi d'étudier [illegible] chez les enfants soumis au traitement [illegible] avait donné comme [illegible] qui inhibe la [illegible] avait pas aussi une influence défavorable [illegible] des cellules de l'hôte en active prolifération [illegible] du sang.

[illegible] des cas (plus d'une certaine) nous n'avions assisté à [illegible] atténuées, ni à des modifications de la biopsie [illegible].

Cette fois le contrôle radiologique du thorax nous a révélé, à côté de [illegible] plus évidemment calcifiés, une opacité remarquable des côtes, de la clavicule et de l'humérus bilatéralement.

Nous avons étendu alors l'examen radiologique à une grande partie du squelette et avons été surpris de nous trouver devant le [illegible] d'une ostéosclérose, qui nous a rappelé d'abord (avec des différences importantes) l'ostéopétrose ou maladie d'Albers-Schönberg.

Le crâne présente un épaississement remarquable de tous les os, surtout de la base (apophyse basilaire de l'occipital et du sphénoïde sont déformées de la selle turcique) et du frontal fourchet de l'apophyse orbitaire et du toit de l'orbite) qui est probablement responsable de la convergence des bulbes oculaires (fig. 2 et 3).

Le *thorax* démontre des côtes uniformément opaques, sans structure trabéculaire sauf à l'extrémité antérieure et postérieure.

Les *corps vertébraux* sont opaques aux rayons en correspondance des

Fig. 2. Pendant le surdosage des vitamines A et D: Epaississement diffus du crâne, surtout de la base.

Fig. 6. Les points où du pied pénètrent autour du noyau central ostéosclérotique une zone périphérique transparente qui correspond à l'un de plus récents formations: os basilaire et pétreux.

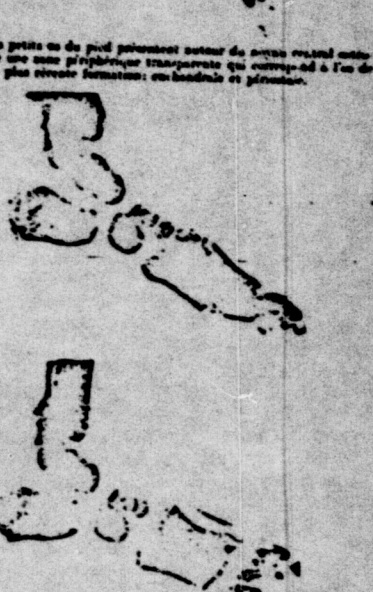

Fig. 7. Après la suspension du surdosage des vitamines A et D. Normale structure osseuse.

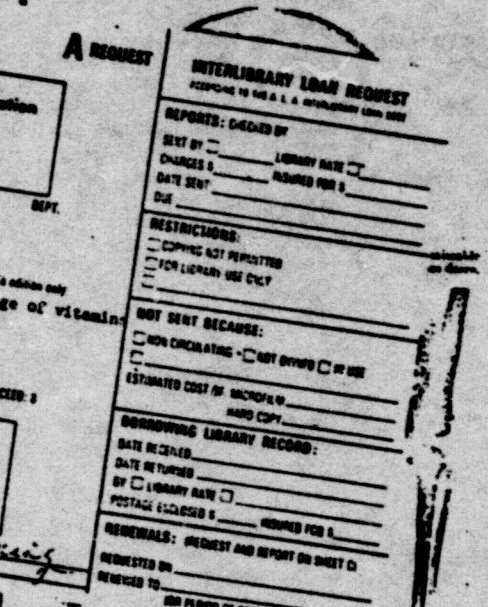

Fig. 4.

Fig. 4. Epaississement ostéosclérotique des diaphyses [illegible] os longs, qui s'arrête au niveau des métaphyses, où la structure osseuse est normale ou même hâtistérique. Ostéite [illegible] épaisse autour des noyaux épiphysaires.

Fig. 5. Après la suspension du surdosage des vitamines A et D. Normale structure osseuse, disparition du canal médullaire.

diaques épiphysaires supérieur et inférieur, mais dans toute leur hauteur. Les [illegible] calcaires se trouvent au niveau de la rate.

Les os plats du thorax sont fortement épaissis sauf une mince couche périphérique où l'épaississement est absent. Le tissu spongieux du [illegible] peut présenter hâtistairement un aspect moins épaissi (pas d'infiltration du tissu [illegible], pas de tissu vasculaire).

Les os longs des membres présentent un épaississement ostéosclérotique de la diaphyse avec épaississement de la corticale compacte qui rentrent le canal médullaire sans toutefois l'oblitérer. L'aspect ostéosclérotique s'arrête avec une démarcation très nette au niveau des métaphyses, où la structure osseuse est normale ou même peut-être légèrement hâtistérique (fig. 4 et 5).

Hâtistérol ostéite [illegible] épaissi autour des noyaux épiphysaires (inférieur du fémur et supérieur du tibia).

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... Konzentration an Gold oder an Cyan) und bei längeren Zwischenintervallen kann der Cyan-Zusatz die Wirkung des Goldes verstärken. Dies wird zurückgeführt auf die Bildung eines Mischsalz-Gold-Cyan-Komplexes, der die kolloid-osmotische Hämolyse hemmt.

Quantitativer Vergleich der verschiedenen Komplexbildner zeigt vor allem die grosse Ueberlegenheit des BAL, in Uebereinstimmung mit den Erfahrungen der Therapie.

Auch die Hemmung läßt sich durch Komplexbildner rückgängig machen, und zwar, im Gegensatz zu den Verhältnissen bei der kolloid-osmotischen Hämolyse, unabhängig vom Zeitintervall zwischen Goldsalz-Zusatz und Komplexbildner-Zusatz. Darin wird ein weiterer Hinweis auf die Verschiedenartigkeit der Angriffspunkte für die beiden Effekte gesehen. Auch hier steht BAL in bezug auf die maximale Wirksamkeit an der Spitze der geprüften Komplexbildner.

1. *Berkhahn, H.*, und *Kraus, W.*: Biochem. Z. 169, 226 (1926). – 2. *Bickel, G.*: Le Journal de Thérapeutique Clinique. 1947, N. 223. – 3. *Hausher, S. H.*: Proc. Soc. exper. Biol. a. Med. (Am.) 28, 310 (1930). – 4. *Meesgeers, E.*: Biochem. Z. 131, 38 (1922). – 5. *Schaff, F.*: Diss. Bern 1949. – 6. *Wilbrandt, W.*: Pflügers Arch. 241, 249 (1938). – 7. *Wilbrandt, W.*: Pflügers Arch. 244, 637 (1941). – 8. *Wilbrandt, W.*: Pflügers Arch. 245, 22 (1941). – 9. *Wilbrandt, W.*: Pflügers Arch. 250, 360 (1943). – 10. *Wilbrandt, W.*: Helv. physiol. Acta 6, 234 (1948). – 11. *Wilbrandt, W.*: Arch. exper. Path. (D.) 212, 6 (1836). – 12. *Wilbrandt, W.*, und *Wyss, H. U.*: Helv. physiol. Acta 5, 457 (1947).

Clinique Pédiatrique de l'Université de Rome – Directeur: Prof. G. Frontali.

Syndrome ostéosclérotique et surdosage de vitamines A et D

Par G. Frontali

Le surdosage de vitamines liposolubles est signalé avec une fréquence croissante. A l'étude expérimentale et clinique de ces conditions ont contribué de mes collaborateurs *Preti, Melagazzi, Nichele, Cortellini* à côté de nombreux auteurs étrangers.

Entre autres se distingue pour sa singularité un cas qui se prête à quelques considérations théoriques et pratiques d'une certaine importance.

Liliana C. di Edmondo, T. A. M., 2 de 4 ans, a été accueillie à la Clinique le 3 février [illegible] en avril 1948 à l'âge de 10 mois, parce que depuis 2 mois [illegible] avec maximum le soir jusqu'à 38–39° C, elle toussait et [illegible].

Le poids à cette première entrée, était de 6,1 kg (comme à 3 mois) et la stature [illegible] cm (comme à 7 mois). Elle présentait les signes de Do la [illegible] et une modeste hépato-splénomégalie.

[illegible] de Mantoux (1:1000) était fortement positive [illegible].

[illegible] se révéla en dehors d'une ostéopathie trachéobronchique, une [illegible] pulmonaire diffuse.

[illegible] donnait un liquide n.a. normal, sous pression normale.

[illegible] d'autre constante, pas même d'albumine indosable, absence [illegible] au moment des cylindres hyalino-granuleux.

[illegible] était de tuberculose miliaire aiguë, le *traitement* de [illegible] par pot, par voie intramusculaire.

A côté [illegible] spécifiques des drogues plutôt hauts de vitamine A (Axer [illegible] d'Axeril en dessus U.I.) et moins élevés de vitamine D (Oleum Sol, 1 ampoule chaque 20 jours = 40 000 U.I. par [illegible].

Pendant ce traitement nous avons assisté à un nettoyage graduel de la [illegible] pulmonaire, avec l'exception de quelques rares noyaux [illegible] calcaire. En atteignant le foie et la rate se sont [illegible] normales. Les urines se sont normalisées. L'[illegible] avait [illegible]%.

En [illegible] temps [illegible] et s'aventurant une anémie hypochrome [illegible] Hb. 42%, index glob. 0,9, globules [illegible] mono. 3%, eosino. 2%, baso. 0%, lympho. 37%, [illegible].

Le myélogramme démontrait une activité érythropoïétique réduite [illegible] maturation de la série rouge et un quotient [illegible] haut: 2,5.

[illegible] hémoculture, 1er myélo, 1er pneumo, 2e [illegible] staphylo. N. 4e [illegible] coagulase N. 4e [illegible] coagulase N. 4e [illegible] coagulase

...ns de la moelle hématopoïétique. Ce double ... est le fondement de la comparaison avec ... En effet, dans les deux cas à la rétraction de l'arti... correspondent des altérations ... des pièces squelettiques, dues à une hypocalcification qui en efface la structure trabéculaire avec une réduction progressive du canal et en général des espaces médullaires.

Mais une comparaison plus attentive révèle des différences essentielles dans les zones si nettement du tissu osseux. En effet dans l'ostéo-porose la plus forte densité de l'hypocalcification se trouve précisément dans les zones d'accroissement juxta-épiphysaires et s'étend d'ici à toute la longueur de l'os, en respectant en partie le canal médullaire. Elle se trouve aussi au niveau de la ... corticale compacte.

Dans les stades plus avancés de l'ostéoporose, toutes les pièces squelettiques acquièrent la densité et l'absence de structure propre des os de marbre ou de plâtre.

L'invasion du périoste ostéo-sclérotique ne réduit pas seulement la cavité médullaire, mais aussi le diamètre des canaux nutritifs, en réduisant les possibilités de nutrition du tissu osseux, qui présente des zones de nécrose et, en conséquence, des fractures spontanées surtout là où il subit des traumatismes, comme par exemple au niveau du col du fémur, où se produisent des infractions et des fractures, dont il sera fait mention dans notre cas.

Par comparaison je considère utile de présenter un cas authentique d'ostéo-porose (maladie d'Albers-Schönberg) que j'ai eu l'occasion d'étudier en 1932 et qui n'a pas encore été publié.

Il s'agit d'une enfant de 12 ans née à Civitale (Frioul) de parents apparemment normaux. Dès l'âge de 16 mois elle avait présenté un pied varus-équin. La deuxième année elle avait souffert pendant environ 4 mois d'une fièvre ... La dentition a été tardive puisque seulement à l'âge de 2 ans et demi.

Peu ou suspect de lues elle avait subi un traitement antisyphilitique (frictions mercurielles, injections d'arsenobenzol et de bismuth) sans avantage.

Vers l'âge de 4 ans elle a présenté une fracture du tibia gauche, puis de celui de droite et encore des os de l'avant-bras gauche (avec pseudarthrose d'un fragment), pour des traumatismes minimes.

Examen clinique: les os du crâne présentent une épaisseur augmentée, surtout l'apophyse orbitaire du frontal, le sphénoïde (sans déformation de la selle turcique) et de la fosse sphénoïdale supérieure) et l'apophyse basilaire de l'occipital.

Les os longs présentent des épaississements calcaires avec ébauche de rétrécissement du canal médullaire. Cependant à différence du cas précédent l'épaississement intéresse surtout les métaphyses et les zones cartilagineuses juxta-épiphysaires. La diaphyse présente des infractions. L'aspect radiologique des vertèbres est caractéristique: les disques épiphysaires supérieur et inférieur sont hyperradiques (zone d'accroissement carbonaté), tandis que les autres parties du corps vertébral sont plus transparentes.

Très remarquable particulièrement est le cas entre autre chez périphériques, sous forme par rétraction du col fémoral. La déformation amorcée qui en devient avant été interprétée par erreur comme due à une luxation congénitale de la hanche et avait même conduit à l'application d'un plâtre.

L'examen radiologique des bassin ne présente épaissie en masse avec contours irréguliers dus à une pseudo-apposition osseuse. Fracture au tiers inférieur du fémur gauche avec col insuffisant.

Fig. 8 vue de face. Ostéoporose. Epaississement des os du crâne, surtout de la base et de l'apophyse orbitaire du frontal.

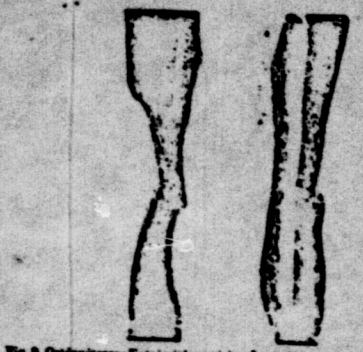

Fig. 9. Ostéoporose: Extrémité supérieure et inférieure du tibia présentant des épaississements en manque avec effacement des structures osseuses, fractures entre l'os épaissi et l'os friable.

Les extrémités supérieure et inférieure du tibia présentent des épaississements analogues en manque avec effacement des structures osseuses. Une fracture entre le tiers moyen et inférieur du tibia droit se trouve située à la limite entre l'os épaissi (privé de structure) et l'os friable.

Une fracture se trouve aussi au tiers moyen du radius droit, avec formation d'un angle obtus entre les fragments.

Moins et pleurs: opacité ne respectant pas les zones juxta-épiphysaires, sans autre chose.

Examen du sang: globules rouges 2 600 000, Hb. 60%, v. gl. 0,88, gl. h. 0,68. Anémie hypochromique avec leucopénie; légère prévalence des neutrophiles; légère érythroblastémie orthochromatique (2%), métamyélocytes (3%).

Calcémie: 9–9,2 mg%. Phosphatémie: 3,8–3,6 mg%. M.R. –15%.

Malgré les analogies entre les deux cas nous avons déjà fait allusion à certaines différences surtout au sujet du compartiment presque opposé des épaississements calcaires en correspondance des zones d'accroissement enchondral et sous-périostal.

Mais la différence plus évidente doit encore être illustrée.

A la 3e rentrée du premier cas à la Clinique nous avons été surpris par la régression presque totale des manifestations du type ostéosclérotique, qui pouvaient être à peine reconnues dans quelques pièces squelettiques.

L'épaississement des os de la base crânienne est encore reconnaissable. En comparant ce résultat à la condition antérieure, on a l'impression que l'opacité se soit dissoute comme du sucre dans l'eau.

Un léger épaississement ostéoplastique des trabécules osseuses reste diffus dans plusieurs segments squelettiques (corps vertébraux, côtes, diaphyse des os longs). Mais le canal médullaire est réapparu. La normale structure osseuse s'est substituée à l'aspect marmoréen (sans structure) que les os présentaient auparavant à l'exception des parties de plus récente formation.

Malgré la normalisation du cadre squelettique l'*anémie* persistait encore.

Examens du sang: gl. r. 2 870 000, Hb. 65%, v. gl. 1,1, gl. h. 7200, N 68%, E 1%, B 1%, L 25%, M 4%. Plaquettes: 140 000 par mm³.

La pauvreté globulaire est prédominante.

Le *myélogramme* révèle encore un manque de cellules progénitrices de la série rouge et une maturation inhibée, tandis que les éléments de la série blanche sont plus abondants et montrent une bonne maturation:

Mégaloblastiques –, hémocytoblastes 1,2%, myéloblastes 2%, promyélocytes X 4,8%, E 0,4%, myélocytes X 10%, E 12%, métamyélocytes 43,2%, E 1,6%, prérythroblastes 1,6%, érythroblastes B 6%, P 21,2%, O 0,4%, Mégakaryocytes 0,4%, caryocinèses rouges 1,6%, cell. plasmatiques 0,8%, Rapport blanc-érythropoïétique 1,6%.

Il faut ajouter les manifestations d'une *néphrite chronique*: albuminurie, hématies et cylindres dans le sédiment.

Anatomie: très élevée (1,10%).

Pression artérielle: 160–180 mm Hg.

Epreuves de division et d. concentration: hypo-sténurie.

Résistance capillaire: présence petits hémorragiques pour –10 cm Hg.
Examen ophtalmoscopique: papilles pâles, vaisseaux minces.
Epreuves des fonctions hépatiques:
Protéines du plasma: totales 5,43%, albumine 2,67%, globulines 2,66%, fibrinogène 0,49%, (hypoprotéinémie, valeurs de la cholestérine et des phosphates très pauvres).
Réaction de Takata: positive.
Courbe glycémique en plateau avec traits ascendant et descendant très hauts.
Bromsulfo-phtaléine: positive.

Ces altérations métaboliques, rénales, hépatiques, démontrent des modifications moins rapidement réversibles que l'hypocalcification squelettique.

Mais qu'est-ce qui est intervenu entre la 2e et la 3e rentrée en Clinique de notre première cas? Seulement la suppression du traitement à hautes doses avec la vitamine A.

Nous avons cherché à nous rendre compte des influences possibles de ce facteur.

A ce propos les données hémorrhagiques ont révélé des conditions normales:

Ca: 9 mg%, *P:* 4,3 mg%.
L'épreuve de Rothera (Ca dans les urines) était normale.
Bilans minéraux du Ca, du P et du K ont été positifs (rétention de Ca 20%, de P 60,8%, de K 38,7% par rapport à l'ingestion).

La vitamine A a été déterminée par la méthode de *Clausen* et *McCann*:

à jeûn: vitamine A 120 U.I. par 100 cm³, correspondant 28 U.I. %
après introduction de 120 000 U.I. par voie orale:
après 2 h.: vitamine A 400 U.I. par 100 cm³, correspondant 120 U.I. %
après 6 h.: vitamine A 720 U.I. par 100 cm³, correspondant 161 U.I. %
après 9 h.: vitamine A 660 U.I. par 100 cm³, correspondant 136 U.I. %

Après 9 heures il y a eu une augmentation de 4½–6 fois les valeurs à jeûn.

Ces valeurs, tout en n'étant pas très hautes, témoignent néanmoins avec une forte élévation après l'introduction (plus forte que normale) l'état de saturation des organes de réserve très que le foie, qui présente des altérations des fonctions de la cellule hépatique.

Il faut considérer que l'administration d'Axérol pratiquée dans la Clinique et surtout les doses plus massives d'Axérol Alpha données à domicile ont trouvé dans notre cas, comme dans celui des deux jumeaux de *Molaguzzi* pour l'intoxication par vitamine D_2, une susceptibilité particulière.

Quelle importance pouvons-nous attribuer dans notre cas aux doses de D_2?

Pour ce facteur les doses quotidiennes, non supérieures à 20 000 U.I. et de 600 000 U.I. tous les 20 jours, sont généralement bien tolérées. Lorsqu'elles ne le sont pas, les manifestations toxiques du surdosage de vitamine D_2 sont différentes: anorexie, polydipsie, hypercalcémie (de haut degré, jusqu'à 16–18 mg%), épreuve de Sulkowitch (pour le calcium urinaire) positive, calcifications extra-squelettiques.

Mais elles doivent lieu aussi à des lésions rénales avec hyperazotémie.

Dans notre cas nous avons eu un syndrome ostéosclérotique réversible, une rétraction avec réduction de l'activité érythropoïétique, une lésion rénale avec hyperazotémie et hypersécrétion acidurée, tandis que la calcémie était normale et l'épreuve de Sulkowitch négative.

Nous ne pouvons pas exclure qu'un surdosage de vitamine D_2 ait pu contribuer à déterminer quelques manifestations de notre cas, surtout celles qui ont intéressé le rein. Mais le syndrome ostéosclérotique, réversible après la suspension du surdosage de vitamine A, nous semble attribuable plutôt à celui-ci.

En considérant la littérature, nous avons pu recueillir 16 cas d'*hypercalcémie* certainement attribuable au surdosage de vitamine A. La première communication de *Collip* (1930) suivie par celle de *Toomey* et *Marriotte*, de *Kugel* et coll., nous montrent des manifestations cutanées assez différentes de celles de notre cas. Il s'agirait le syndrome de Collip (selon *Rosenblum* et *Gorodnyi*) se produisant – au dessous de 4 mois – même indépendamment d'un surdosage de vitamine A.

Notre cas a une place à part pour la rapidité de ses manifestations, pour son atrophie et ses différences relatives avec l'ostéoporose d'Albers-Schönberg et pour les considérations pathogéniques que cette comparaison suggère par rapport à la fonction ostéoplastique et hématopoïétique dans les deux formes d'ostéosclérose.

Cette observation, comme celles qui l'ont précédée au sujet du surdosage de vitamine D_2 et D_3, doivent conseiller, on peut le voir pratique, d'indiquer sur l'emballage des produits contenant ces vitamines, non seulement les doses thérapeutiques efficaces, mais aussi les doses non-nocives, au delà desquelles la course ne devient dangereuse.

Résumé. L'auteur décrit, à propos d'un exemple, un syndrome ostéosclérotique (réversible), lié à un surdosage de vitamines A et D, différent de l'hyperostose corticale de *Caffey* et *Kugel*.

En antithèse il présente un cas d'ostéoporose (maladie d'Albers-Schönberg), en dégageant de la comparaison et des différences essentielles entre les deux affections des considérations d'importance théorique et pratique.

Caffey: Pediatrics 1930, 5, 672. – *Rotegard:* Pediatrics internat. 1932, 9, 105. – *Nobel* et *Cantarini:* Pediatrie internat. 1932, 9, 65. – *Petersen:* J. Pediatr. (Am.) 1930, 32, 202. – *Pease:* Jour. Am. Med. Assoc. Febrero 19, 1932. – *Josephson* et *Greenberg:* Amer. J. Dis. Childr. 1932, 4, 702. – *Kugel, Pease* et *Stevenson:* Amer. J. Dis. Childr. 1932, 4, 203. – *Toomey* et *Marriotte:* Amer. J. Dis. Childr. 1932, 672.

Zeitschriftenreferate

Bakteriologie

Über ein Gebärmutter des spheroïdes de Thorent aus une ... Von H. C. Vogt. Schweiz. Z. Path. 14, 1, 36 (1934).

Zur Kenntnisfrage der Biologie des Pfeiffer-Influenzabazillus. ... Von ... Z. Path. 14, 1, ... (1934).

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Action tuberculostatique de l'o-Phénanthroline. Von G. Tarsia. Schweiz. Z. Path. 14, 1, ... (1934).

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Contribution à l'étude des Leptospiroses bovines en Suisse. Von Theodor Wiesmann. Schweiz. Z. Path. 14, 1, 93 (1934).

Bei 65 von 200 untersuchten, anscheinend gesunden Rindern aus verschiedenen Gegenden der Schweiz konnten im Serum Agglutinine und Lysine gegen L. pomona nachgewiesen werden. Die 65 positiven Sera verteilen sich folgendermaßen: 30 mit L. icterohaemorrhagiae und L. pomona, 2 mit L. pomona, 1 mit L. australis und 1 mit L. grippotyphosa. Die Arbeit zeigt erneut die Häufigkeit der Rinder-Leptospirosen und bestätigt den Feststellungen von Wiesmann über die besondere Rolle von L. icterohaemorrhagiae als Agenzien in bovilinen Form von L. Hoff, der auch in vitro als wirksamen Tuberculostatikum erwies. Es kommt zu spezifischer Zuchtung des Wirkstoffs von Tbc.-Bazillen bei einer Verdünnung 1 von 1: 2 500 000. H. R. Marti, Zürich

Action tuberculostatique de l'o-Phénanthroline. Von G. Tarsia. Schweiz. Z. Path. 14, 1, ... (1934).

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FOOD AND DRUG ADMINISTRATION
FEDERAL SECURITY AGENCY

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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HYPERVITAMINOSIS A

SANFORD E. GOLDBERG, II, M.D., JOHN C. PHAGANO, M.D., AND
ARNOLD M. WALD, M.D.
NEW YORK, N. Y.

SINCE 1944 when Josephs[1] first reported the syndrome of hypervitaminosis A in man, reports have appeared with increasing frequency until at present twenty-three such cases are recorded.[1-12] Briefly, the components of the syndrome[2] in children are: cortical thickening of the involved long bones with pain and swelling over them, hyperirritability, pruritus, rash, cheilosis, changes in the hair ranging from coarseness to alopecia, and, on occasion, bleeding tendency. The diagnosis is established by finding an elevated serum vitamin A level.

CASE REPORT

W. M., a 24-month-old female, born on March 4, 1950, was seen on Feb. 27, 1952, because of skin rash, hyperirritability, and forearm tenderness. The patient had been well until the age of 14 months, when she became bowlegged. Films of her legs and arms, at 16 months, showed only slight bowing of the tibias (Fig. 1). At 18 months, she lost her appetite and failed to gain weight. Approximately three weeks later, a generalized itchy rash appeared which was more marked on the extensor surfaces of the extremities. Hyperirritability was noted at 21 months. At 22 months, an orthopedic surgeon suspected early tibia vara,[13] prescribed corrective shoes, and told the parents to "Give the youngster an adequate vitamin A intake." At this time, the child's legs and feet were exquisitely tender. One month later, this tenderness had subsided, but her forearms had become painful. Fever, hair changes, cheilosis, or hemorrhagic manifestations never were apparent.

The patient was a first-born child, delivered normally at term. Early growth and development were normal prior to the fourteenth month.

Feeding History.—The infant was breast fed until the age of 6 months when she was changed to formula. Orange juice was started at age 2 weeks, one ounce daily. This was gradually increased until at 18 months she received eight ounces daily. Oleum Percomorpheum* was started at 3 weeks, four drops a day. This was continued until age 3 months when the dose was increased to six drops a day. At 7 months, the child was given ten drops daily. This was continued until age 18 months, when the dose was increased to four dropperful (120 drops) daily. At 22 months, the dose was increased to eight dropperful, which was continued until the twenty-fourth month. The mother stated that she increased the dose on her own initiative in the hope of improving her child's appetite.

Physical examination revealed a very irritable, uncooperative and slightly undernourished 24-month-old female child who complained bitterly when her forearms were touched. The skin over the anterior surfaces of the arms, legs, buttocks, and lower abdomen was dry, coarse, and scaly, and had numerous scratch marks. The forearms presented long, spindle-shaped swellings on the lateral surfaces of the ulnas. The swellings were of bony consistency, and were attached to the bone; the overlying skin was freely movable. The tibias were bowed, but were not tender or swollen. The child was afebrile; the head was symmetrical, with no frontal bosses or mandibular swelling. The hair was normal in

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*One drop of Oleum Percomorpheum contains 1,250 units of vitamin A and 150 units of vitamin D.

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texture. Sixteen normal teeth were present. The upper respiratory tract, heart, and lungs were normal. The liver was palpable one fingerbreadth below the costal margin. The abdomen was normal.

Laboratory Findings.—On Feb. 27, 1952, the serum vitamin A level was 100 blue units per cent (normal up to 20); the total carotinoids was 80.0 units per cent—normal 50 to 100. On March 6, one week after vitamin A was discontinued, serum vitamin A level was 20 blue units per cent; total carotinoids was 73.5 units per cent. Serum calcium was 8.6 mg. per cent, serum phosphorus 4.6 mg. per cent, and serum alkaline phosphatase 6.8 Bodansky units. The hemoglobin was 11.0 grams, red blood count 4.1 million, white blood count 8,800; the differential count was 59 polymorphonuclear cells, 3 monocytes, and 38 lymphocytes. Urine contained 7 to 10 white blood cells per high-powered field, and one-plus albumin. Subsequent catheterized urine specimen had no albumin or cells. On March 18, cephalin flocculation test was negative, thymol turbidity was 1 unit, and serum bilirubin was 0.015 mg. per cent. Total serum protein was 8.4 grams per cent, serum albumin 5.4 grams per cent, and globulin 3.0 grams per cent.

Roentgenographic Findings.—In February, 1952, roentgenographic examination of the entire skeleton disclosed bilateral symmetrical cortical thickenings of the ulnas, the anterior surfaces of the tibias, and the second to fifth metatarsals (Fig. 2 *A-C*). The cortical thickenings were most prominent in the ulnas where the distal two-thirds of the shafts were affected. The changes in the ulnas corresponded exactly to the tender swellings in the forearms. The skull, mandible, clavicles, vertebrae, fibulas, and the remainder of the long bones were not involved.

A. *B.*

Fig. 1.—Roentgenograms at 18 months of age, before the ingestion of excess quantities of vitamin A. *A*, The radii and ulnas appear normal. *B*, The tibias are slightly bowed and demonstrate the structural changes usually associated with bowing, i.e., thickening of the concave side.

Clinical Course.—Immediately after the diagnosis was confirmed roentgenographically, all intake of Oleum Percomorpheum was discontinued. Forty-

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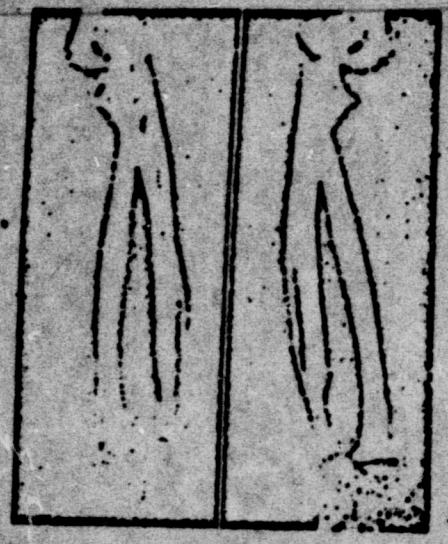

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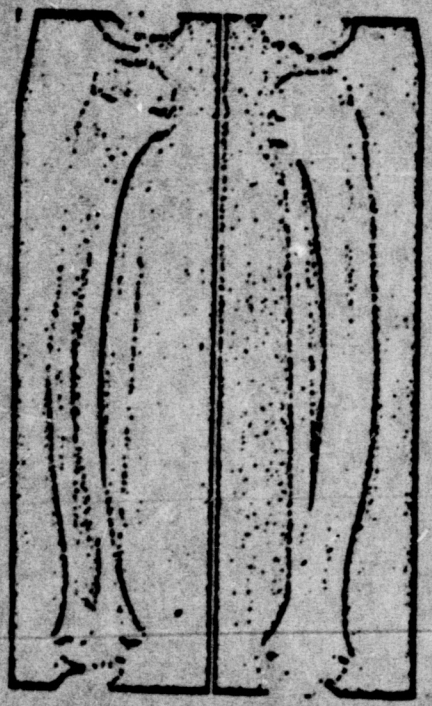

B.

C.

Fig. 2.—Roentgenograms at 24 months of age, after the ingestion of toxic quantities of vitamin A. *A*, Bilateral symmetrical cortical thickening of both ulnae is present. *B*, The tibiae are thickened anteriorly. *C*, Bilateral symmetrical cortical thickening of the shafts of the second to fifth metatarsals is demonstrated.

eight hours later, hyperirritability and bone tenderness were greatly diminished; after seventy-two hours, the pruritus was considerably relieved. Within seven days after discontinuing vitamin A, tenderness, hyperirritability, and pruritus were barely perceptible, and the rash had begun to clear. After fourteen days, the child was asymptomatic, and the rash was almost completely cleared. This child was treated on an outpatient basis during the entire clinical course.

COMMENT

The striking clinical features of this patient—hyperirritability, rash, and swelling of the ulnar aspects of the forearms—suggested the diagnosis of hypervitaminosis A immediately. Specific inquiry regarding the use of vitamin preparations elicited the history of excessive ingestion of Oleum Percomorpheum.

We were able to obtain quick roentgenographic confirmation of the diagnosis, and felt that hospitalization was unnecessary while awaiting the result of the blood vitamin A level determination. Treatment at home consisted of withdrawal of vitamin A and application of calamine lotion. The

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quick return to normal of the serum vitamin A level is unusual. We were fortunate in having films taken before the ingestion of excessive vitamin A (Fig. 1). They serve to demonstrate graphically the marked selective bony changes which this disease is capable of producing.

With increasing awareness of the clinical entity of hypervitaminosis A,[10] cases are being recognized and diagnosed with greater frequency. We are reporting this case to supplement the statements already made regarding the potential toxicity of vitamin A and the desirability of proper safeguards being adopted in labeling all preparations containing vitamin A. The label should state the proper dose and warn mothers of the danger of overdose. It is appropriate at this point to note that the increased vitamin D intake usually accompanying excess vitamin A ingestion is not believed to be a pathogenic factor.[9, 11] Furthermore, this child manifested no symptoms or signs usually associated with hypervitaminosis D.[11]

CONCLUSIONS

1. An additional case of chronic poisoning due to the excessive administration of vitamin A is reported.
2. Further evidence of the necessity of proper labeling of the many easily available and commonly used vitamin A preparations is presented.
3. Prompt recognition and early diagnosis of this condition will avoid unnecessary hospitalization and expense.

We wish to express our appreciation to Dr. John Caffey who has reviewed our films and found them similar in every respect to the previously reported cases.

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MEDICAL INTELLIGENCE

VITAMIN A INTOXICATION

Report of a Case in an Adult

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INTOXICATION from overdosage of vitamin A is suggested by the following recognized signs and symptoms: anorexia, irritability, generalized pruritus, painful extremities, arthralgia and sparse, coarse hair.[1] Hepatomegaly and splenomegaly coupled with hypoplastic anemia, clubbing of fingers, and an abnormal appetite for butter and fish oils have been recorded. It is interesting that similar symptoms develop in rats given toxic doses of vitamin A. The fact that until recently vitamin A intoxication has been reported only in infants and children is not surprising; it is this group that receives supplemental vitamin A in a variety of fish oils or concentrates. The conscientious mother may unwittingly overdose her child under the misconception that "if a little is good, a lot is better." The older child may develop a taste for one of the fish oils and overdose himself by overindulging.[1] Mothers using supplemental feeding of vitamin A for their children should be informed of this hazard; the fact that the adult daily requirement of vitamin A[2] is between 2000 and 4000 units, and that of children about half this amount, should be widely publicized.

Vitamin A intoxication, however, is not limited to infants and children. Sulzberger and Lazar[3] recently described this syndrome in an adult who was inspired to self medication with large doses of vitamin A by a radio "nutrition commentator." In its major clinical manifestations the syndrome appears to be the same whether it occurs in children or in adults. During a prolonged course of vitamin A therapy for generalized desquamation, the patient described below manifested the characteristic signs of hypervitaminosis. This case again emphasizes and confirms the opinion of previous authors[3] that "physicians administering large doses of vitamin A must be on the lookout for signs and symptoms of toxicity."

CASE REPORT

Mrs. A. S., a 52-year-old woman, was first seen on February 29, 1952, in consultation at the request of her physician to ascertain the cause of spontaneous bleeding from the mucous membranes.

Since childhood she had had generalized flaking of the skin. About 4½ years previously cracking and oozing about the eyes and of the legs had developed. When various treatments did not give relief, her physician placed her on a regimen of vitamin A therapy. In the early part of 1945 she received 150,000 international units of vitamin A and 100 mg. of antihistamine daily for the 1st week and 100,000 units of vitamin A daily thereafter. (The latter dosage of vitamin A was taken from the early part of 1948 until February, 1952.) Within 1 month the weeping lesions of the legs cleared, but the desquamation of the skin remained.

In the early part of 1949 she began to suffer from insomnia. By the middle of the same year she felt "out of sorts" and listless but had no specific complaints. Toward the end of the year she noted great difficulty in keeping her hair groomed. In the early part of 1950 she had lost a considerable amount of scalp hair but also noticed loss of hair from the eyebrows and eyelashes, and from the axillary and pubic areas.

By October complete loss of hair from the eyebrows, eyelashes and axillary and pubic areas had occurred. The scalp hair had so thinned that the whole scalp was visible. From then until June, 1951, she began to have stiffness and pain in the joints of the fingers, elbows, shoulders, hips, knees and ankles. At no time, however, did she experience any throbbing, heat or swelling of any joint. Her housework now became too difficult to accomplish. At about this time her husband made the observation that a small patch of skin on the forehead appeared "dirty like" and that his wife's eyes were somewhat more prominent than usual.

Concomitantly with the onset of joint pains, there was a progressive loss of weight and appetite. The patient became completely disinterested in her surroundings and appeared "to brood all the time." Because of a possible relation of pyorrhea to her joint symptoms, she was advised to have all her teeth extracted. Her upper teeth were extracted in June. Extraction was followed by immediate severe hemorrhage and continuous bleeding, even after suture of the gums. However, the surgeon gave vitamin K empirically immediately after operation for a number of injections, after which the bleeding subsided. Thereafter she received a weekly injection of vitamin K and liver from her attending physician. These injections were continued until October.

From June to October she also received a course of cortisone therapy for 12 weeks, without improvement in the joint symptoms. At about this time she began to note severe aching "in the bones" of both upper and lower extremities that was different from the pains in the joints. With the onset of aching in the bones of the extremities, locomotion became impossible because she could not stand for more than a few moments at a time.

In October she was admitted to the hospital for extraction of the lower teeth. Because of the previous history of bleeding after extraction of the upper teeth, she was given empirically an injection of vitamin K preoperatively. Although hemorrhage immediately followed extraction of the teeth, she experienced no further bleeding after suturing of the gums.

By November she had lost over 30 pounds in weight and her appetite was "almost completely gone." At this time her attending physician prescribed 2 vitamin capsules a day. Toward the middle of December she began to note a "thumping headache." By the middle of January, 1952, spontaneous oozing of blood from the nose and a mild irritation of the eyes began. About 3 weeks later the eyes were quite inflamed. At about this time she noted oozing of blood not only from the nose but also from the mucous membrane of the right eye and left external ear canal.

From 1949 to 1951 there had been irregularity of the menstrual periods and occasional bouts of hot flashes. Since March, 1951, there had been no menstrual bleeding.

Physical examination showed the patient to be pale and chronically ill. The scalp hair was coarse, dry and brittle and appeared unkempt, and there was a loss of a great amount of hair. The hair of the eyebrows and eyelashes was completely lacking. Above the glabella there was an area a few centimeters of light brownish pigmentation. The eyes revealed obvious prominence and puffiness. The conjunctivae demonstrated an ulcerative blepharitis without any secretion or blood from the left. Eyeground examination

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d abnormal pulsations of the retinal veins, more so on ight than on the left. Oozing of blood was noted from mucous membranes of the nose and external canal of ight ear. There was a generalized fine desquamation e skin. The scalp evidenced a moderately severe seborAxillary hair was completely lacking. Neither the nor the liver was palpable. Pubic hair was also lackVaginal examination was negative except that immey after examination a generalized oozing of blood was from the vaginal mucosa. There was pain on passive ire flexion or extension of any joint. Marked tenderas elicited over the long bones of all extremities on ion. None of the joints revealed any swelling or ity.

previous hospital admission on October 26, 1951, the obin was 11 gm. per 100 cc., and the white-cell count ith a normal differential count. At this time a bleed- of 2 minutes and a coagulation time of 4½ minutes nd before injection of vitamin K. Examination of d on February 29, 1952, showed a red-cell count of 0, with a hemoglobin of 10.5 gm. per 100 cc., and a l count of 6,900, with 3 per cent rod and 47 per cent d neutrophils, 6 per cent eosinophils, 1 per cent . 41 per cent lymphocytes and 2 per cent mono-

ing February 29, 1952, all vitamin therapy was dis- ; and by the end of 1 week the patient volunteered mation that amelioration of symptoms had oc- The arthralgia and aching in the bones, although ere improving. The bleeding from the mucous s had subsided, and the eyes had cleared. By the cks the aching in the long bones had disappeared, rthralgia had considerably improved. She also egain her appetite and became more interested oundings. At this time, because of annoying pul- aches, she was hospitalized for cerebral angi- The diagnosis of cerebral aneurysm was not con- a sternal-marrow puncture was reported as normal he presence of marked eosinophilia. She was dis- n the hospital without incident.

ths later the patient was free of all joint pains move all extremities freely. There was a full air on the eyebrows, eyelashes and pubic area able new growth of scalp hair; the hair of the was conspicuously lacking. Six months after isit she had regained 30 pounds in weight. She rowth of about 12 long hairs in each axilla; hin and upper lip was also noted. During this mentation of the forehead noticed on the first ad completely disappeared.

nt writing the bilateral exophthalmos has com- d. However, a perceptible pulsation of the persists. On funduscopic examination only e right eye still reveal marked abnormal pul- herger and Lazar[3] noted exophthalmos in ut questioned its connection with the hyper-

nt's early symptoms were insomnia and It was well over a year before she loss of scalp hair. However, beginning ory of loss of hair, the symptoms, par- e referable to the joints, were similar e patient described by Sulzberger and ot that sweats and generalized pruritus erienced. Extraction of the upper ied the danger of hemorrhage from mucous membranes and its correcistration of vitamin K. The relang exophthalmos to vitamin A inny, is unknown. The patient never pulsating headache until a month A therapy was stopped; the headt.

This patient manifested the typical symptomatology; the fact that she was completely relieved of her joint pains and aching bones, with regrowth of lost hair within six months of discontinuation of ingestion of vitamin A, is interpreted as evidence of toxicity of vitamin A ingested in large doses over a prolonged period.

The pathologic processes noted in vitamin A intoxication are the observations recorded from work done on rats. These observations have been summarized in Josephs'[1] article. Rarefaction of bone and thinning of the cortex account for the spontaneous fractures. Although this occurs in the young growing rat under experimental conditions it does not occur in the full-grown animal. An increased excretion of calcium also occurs, but the serum calcium and phosphorus are not affected. In the reticuloendothelial cells, the Kupffer cells of the liver and the spleen an increased deposition of fat is observed. The function of the liver is depressed, and there is a rise in the total lipids. The basal metabolic rate is decreased, but no effect on blood formation is noted in animals.

Swelling and pain of the long bones in the growing infant or child suffering from prolonged overdosage of vitamin A are due to pronounced periosteal thickening.[2] The x-ray appearance of the involved bone may simulate cortical hyperostosis. This does not occur in the adult. Increased total lipid is recorded in human beings. Hypoprothrombinemia and low serum proteins may be explained by liver dysfunction occasioned by increased deposition of fat in the liver. The rise in serum phosphatase that may occur whether implemented by diseased liver or bones is not clearly delineated. The hepatomegaly and splenomegaly may be explained by excess deposition of fat in these organs. Josephs[1] suggests the possibility that pathologic tissue replaced bone marrow to account for the hypoplastic type of anemia that occurred in his case. He also speculates that the occurrence of low basal metabolic rates in these cases is not due to lowered thyroid activity but to the presence of an excess of thyroid antagonist. That a definite relation exists between the thyroid gland and vitamin A is suggested in the summary of the experiment recorded by Sulzberger and Lazar.[3] "It has been demonstrated that the simultaneous administration of vitamin A and thyroxin prevents a rise in basal metabolic rate, that administration of a diet high in cod-liver oil to patients with exophthalmic goiter reduces the basal metabolic rate, that persons with hypothyroidism have low vitamin A levels and that in rats vitamin A causes a decrease in thyroid size and reduces the basal metabolic rate. In a clinical description of patients with vitamin A intoxication these authors allude to the great similarity between the

appearance of the skin in hypervitaminosis and that in hypothyroidism, avitaminosis and hypovitaminosis.

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THE PRACTICAL USE OF A COOLING DEVICE TO INHIBIT THE CUTANEOUS PAIN OF HYPODERMIC INJECTIONS*

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THE pain, discomfort, unpleasantness and anxiety attendant upon hypodermic injections given to children is well known to most physicians, particularly to those, such as pediatricians and allergists, who routinely administer a large number of hypodermic injections. The fear of anticipation is often much worse than the actual pain of the injection and is frequently translated into unpleasant

FIGURE 1. *Automatic Freon Gas Refrigerating Unit (Approximately One Fifth Actual Size.)*

disturbances in the reception room of the office or on the wards and in the outpatient clinics of the hospital. Extreme examples have been noted in children who start to scream as the car in which they are riding approaches or passes the doctor's office, where they have previously been inoculated. Certainly, some children are so emotionally upset by injections that treatment could be termed "worse than the disease." Although I have had no experience with adults, many of them also have a profound fear of "needles" and are quite about receiving hypodermic injections.

With these facts in mind, use of the cooling for inhibition of cutaneous pain, according method of Ingraham, Matson and Wiley their report in 1947, was begun. Over the the various cooling devices have included bottle type with ice, ice and calcium chlo operated freon gas and finally automatic operated freon gas.

While attempts to determine the value an apparatus in practical use were begun the convenient, efficient and economical unit in Figure 1 was devised.§ By means of a of freon gas, seated by the action of screw cap, a measured amount of the gas matically flows into a chamber at the tip of the tip on a firm surface. When the is released the gas is allowed to escape small opening and in so doing cools the temperature of approximately 5°C. in a of about five seconds. The smooth metal the tip is then held firmly against the skin five to sixty seconds, reducing the skin to approximately 11°C. The hypoder is inserted through the cooled skin, and the sensation of needle pressure by contact on the adjacent skin. More than 7000 injections have been given by this meth in the past year. Many of these are in jections on the same patient. The ages dren varied from two to sixteen years below the age of two years were not in this study since subjective results from group could not be obtained and evalua number of injections that could be given gas cartridge varied from 12 to 28, with of 22 during the past year. As the operat familiar with the device and its efficien average number of injections per car creased.

Results

From an entirely practical standpoint the cooling device for inhibition of cutaneo hypodermic injections was eminently both for the doctor and for the patient office practice. It eliminated almost all and unpleasantness for the patient was employed. Results were fairly uni occasional failures being caused by tec ficulties. In several patients there appe complete failure of inhibition of pain w cooling device was used. These were ha tional children with a great deal of and low pain threshold. These are reported

Ingraham, F. D., Matson, D. D., and Wiley cutaneous pain response by local application reducing pain of hypodermic injections. *New* 1947.

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§Developed with the technical assistance of Mr. Robert Peck, of Milton, Massachusetts.

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HYPERVITAMINOSIS A: REPORT OF A CASE IN AN ADULT MALE*

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Ann. Int. Med 39: 131-34 (July) 1953

The syndrome of hypervitaminosis A has been described in at least 17 infants and young children since Josephs' original article in 1944.[1-3] Sulzberger and Lazar[3] described similar toxic symptoms which occurred in an adult female who took large amounts of vitamin A in an attempt to prevent colds. Rodahl[4] has described the toxic symptoms of hypervitaminosis A resulting from polar bear liver ingestion.

The present report is of an adult male with this syndrome and demonstrates several interesting features.

Case Report

Present Illness: A 25 year old Mexican drug store clerk was first seen by us on March 3, 1952. He complained of marked asthenia, a 10 pound weight loss, anorexia, polydipsia, polyuria, a skin rash, excessive loss of the hair of the entire body, soreness and fissuring of the lips, and pain in the area of the shoulder joints, ribs, tibiae and knees. All of his symptoms were of about two weeks' duration. He and his family believed that he was very seriously ill.

Questioning revealed that for about two months the patient had been taking three to four vitamin A capsules daily (50,000 U.S.P. or international units per capsule), and two to three multivitamin capsules daily, each of which contained 25,000 units of vitamin A. He had also taken three ampuls of vitamin C and four or five 1 mm. injections of liver during that period. The patient would often omit a meal and take vitamin capsules in lieu of eating. Shortly after the onset of the above symptoms the patient was seen by a physician in Tijuana, Mexico, who prescribed three injections of cortisone, three ampuls of 2 ml. each of vitamin B complex, and three injections of a sodium salicylate-colchicine, sodium iodide preparation. The patient discontinued vitamin A and all other medications about one week before entering the hospital.

Past History: The patient had been in good health and had had no previous serious illness. He had never had any known liver disorder. Family history was non-contributory.

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RETURN TO MEDICAL LITERATURE BRANCH

Physical Examination: The patient was a well developed, alert, coöperative male looking his stated age of 25. He appeared acutely ill. The significant findings were the following:

1. A patchy alopecia. The hair of the scalp or any part of the body could be pulled out with ease. The patient's pillow-slip and bed linen were also littered with his hair. There were oval areas of alopecia on the legs.
2. A maculopapular rash on the chest, oiliness of the skin on all areas of the body, desquamation of the skin over both heels, and a strong odor emanating from the skin.
3. Slight faucial injection and marked desquamation of the buccal mucous membrane.
4. A sinus tachycardia (rate 100 to 110), though the blood pressure, heart size and sounds were normal.
5. Liver enlarged by palpation three fingerbreadths below the right costal margin, nontender.
6. Marked tenderness over many bones, particularly the left clavicle, the lower ribs and both tibiae.

Laboratory Studies: March 3, 1952: Complete blood count, normal. Fasting blood glucose, 110 mg. per cent. *March 5, 1952:* Red blood count, 3.97 million. Hemoglobin, 12 gm., 84 per cent. White blood count and differential, normal. Total proteins, 7.0 gm. Serum albumin, 3.81 gm. Serum globulin, 3.19 gm. Cholesterol (total), 162. Alkaline phosphatase, 7.0 units. Bromsulfalein, 1.5 per cent retention in 45 minutes. Icterus index, 16. Cephalin flocculation, 1 plus in 48 hours. Bilirubin, 1.6 mg. per cent. Calcium, 13.6 mg. per cent (normal, 9 to 11.5). Phosphorus, 3.1 mg. per cent. Kline and Kahn, negative. *March 10, 1952:* Blood prothrombin time, 14 seconds (control, 17 seconds); concentration, 156 per cent. Blood carotenoids, 23 micrograms per cent (normal, 100 to 225). Blood vitamin A alcohol, 183 micrograms per cent (normal, 20 to 60). *March 18, 1952:* Blood carotenoids, 82 micrograms per cent. Blood vitamin A alcohol, 237 micrograms per cent. Serum calcium, 12.7. *March 28, 1952:* Blood carotenoids, 69 micrograms per cent. Vitamin A alcohol, 153 micrograms per cent. Urine: *March 3, 1952:* Routine analysis, normal. *March 5, 1952:* Bence-Jones protein determination, negative. *March 8, 1952:* Sulkowitch test, "milky reaction" (strongly positive). *March 10, 1952:* Sulkowitch test, normal. *March 18, 1952:* Sulkowitch test, normal.

X-Rays (March 3, 1952): X-rays of the chest, abdomen and skull were completely normal. There was no evidence of osteoporosis or cortical hyperostosis.

Electrocardiogram (March 3, 1952): Normal except for slight tachycardia (rate 104).

Course: The patient received no therapy other than withdrawal of vitamin A and modified bed-rest. He was advised to restrict the intake of butter and cream. The symptomatic improvement was rapid. Two days after he entered the hospital the bone and joint pain disappeared, the appetite returned to normal, and the asthenia was replaced by a sense of well being. The skin rash and the desquamation of the buccal mucous membranes cleared rapidly. The hair continued to fall out and to be coarse and brittle for about three weeks, then it began to grow back and to lose its brittleness. Much of the hair of the eyebrows and eyelashes fell out about two weeks after he entered the hospital.

The liver enlargement decreased gradually. Two weeks after his entry into the hospital the liver was palpable two fingerbreadths below the right costal margin; three weeks after entry it was one fingerbreadth below the right costal margin.

The pulse rate returned to normal about three days after his admission to the hospital.

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The patient was discharged eight days after entry into the hospital and continued to convalesce at home. He rapidly regained the lost weight. About two months after the onset of his symptoms he was clinically well.

Discussion

The essential differences in this case from the similar case in an adult female previously reported are that our patient did not present pruritus, skin pigmentation, exophthalmos or sexual alterations, but did demonstrate hepatomegaly and a greasy odorous skin. Features presented common to cases previously reported in infants and children included bone and joint pain, skin rash, alteration of the mucous membranes of the lips, asthenia, weight loss, anorexia and hepatomegaly.

Factors other than the mere ingestion of large amounts of vitamin A may be involved in the pathogenesis of this condition. Josephs,[1] for example, cited the observation of an eight month old infant who received 500,000 units of vitamin A daily over a period of four months, with no symptoms of toxicity and with a normal blood vitamin A level. All authors have reported complete recovery from this syndrome following withdrawal of vitamin A. Several have repeated experimentally the clinical syndrome after the symptoms had subsided by re-administering high doses of vitamin A.

Rodahl [6] in excellent monographs has reviewed the subject of the toxic effect of polar bear liver and hypervitaminosis A, and has contributed interesting observations on experimental animals. He states that it has been known for centuries among Eskimos and Arctic travelers that the ingestion of polar bear liver by men or dogs causes severe illness. Acute symptoms of severe headache, dizziness, irritability, vomiting and diarrhea occur following the ingestion of polar bear liver. After about a week or more, peeling of the skin and some loss of hair may occur. Rodahl demonstrated by feeding experiments with rats that the large amounts of vitamin A in polar bear liver were responsible for these toxic symptoms.

Conclusion

A case of hypervitaminosis A in an adult male is reported. The patient presented anorexia, weight loss, asthenia, skin rash, loss of hair, polydipsia, polyuria, soreness and fissuring of the lips, bone and joint pain, hepatomegaly and tachycardia. He made a prompt recovery following cessation of vitamin A ingestion. The similarities and differences between this case and the others reported are discussed.

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ACUTE *LEPTOSPIRA POMONA* ARTHRITIS AND MYOCARDITIS*

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A case is reported below of acute arthritis and myocarditis associated with specific serologic reactions of leptospirosis due to *Leptospira pomona*, which resembled rheumatic fever sufficiently closely to require specific diagnostic methods for differentiation. The case presented symptomatology not heretofore described in leptospirosis, and increased the number of clinical pictures that suggest the possibility of leptospiral etiology.

The leptospiroses are a group of illnesses caused by spirochetes of a number of immunologically distinct strains. *Leptospira icterohaemorrhagiae*, the cause of Weil's disease, and *Leptospira canicola*, the cause of canicola fever, were comparatively well known in the United States before 1951. Evidence of human infection with *Leptospira pomona* was first recognized in the United States in 1951.[1] Reports of other cases of *L. pomona* infection soon followed,[2] as well as reports of cases of infection with other strains, namely, *Leptospira autumnalis*[3] and *Leptospira grippotyphosa*.[4] Fourteen different specific leptospirae were recognized by Gsell [5] as a result of studies of the strains of leptospirae and reports of cases and epidemics of illness from all parts of the world. The infections caused two main groups of clinical manifestations. The first group comprised infections that were sometimes severe and often associated with jaundice. They

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ACUTE HYPERVITAMINOSIS A OF THE INFANT

Its Clinical Manifestation with Benign Acute Hydrocephalus and Pronounced Bulge of the Fontanel; a Clinical and Biologic Study

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AND
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CHRONIC hypervitaminosis A accidents are now well known, through the works of Rodahl and Moore and Josephs, and especially through the mainly experimental observations of Toomey and Morisette and, later of Rothman and Leon. There are various publications on this subject in the medical literature.

Our purpose is to draw attention to the acute incidents which may follow the administration of very large quantities of vitamin A in the infant. These incidents are especially characterized by acute hydrocephalus, with spontaneous and intensive bulging of the fontanel, frequent vomiting, agitation, or insomnia, and this without any meningeal sign or disorder in the general status. The disturbances begin 12 hours after ingestion of the drug and end 24 to 48 hours later, spontaneously or after lumbar puncture.

Since we first described, in February, 1951,[1] the syndrome of acute and benign hydrocephalus in the infant following the ingestion of a large amount of vitamin A, the observation has been confirmed by many pediatricians. Some of them remembered infants presenting extreme bulging of the fontanel, vomiting, and normal temperature, but with the cause of the disorder unknown. Informed by our observations, they conducted a written or oral inquiry of the families, and they were able to retrace the ingestion, 24 hours before the incident, of a large dose of vitamin A, plain or associated with vitamin D. Such are the cases reported by S. Thieffry (Paris), in dizygotic twins, and by M. L. Jammet (Paris), l'Hirondel (Caen), and Cluet Garcia[2] (Barcelona). Finally, after our communication, many French and foreign pediatricians observed the syndrome as we described it—in particular, Fleury[3]; Vonderveit, in France; Montero Rodriguez,[4] in Spain; Caruana and Hamza,[5] in Tunisia; Demoulin[6] and Hooft, in Belgium, and Knudson and Rothman[7] (Dr. Mary Mulloy's case), in the United States.

I. ACUTE HYDROCEPHALUS FOLLOWING INGESTION OF LARGE QUANTITY OF VITAMIN A ASSOCIATED WITH VITAMIN D

We shall here report three cases we presented on Feb. 20, 1951, at the Society of Pediatrics in Paris.

CASE 1.—B. Gilles, aged 3½ months, weighing 5,600 gm., on July 7, 1949, vomited at 7 p. m. the feeding he had just drunk. He was pale and fell asleep very soon and did not awaken at

From the Service of Professor Julien Marie, Hôpital des Enfants-Malades, Paris XV°.

10 p. m. for his feeding, although he usually had a good appetite. On the next day the child was gay and drank well, but he was still pale, and the mother noticed a bulge of the fontanel.

The child was brought to the hospital; he was strictly afebrile and looked normal, but his anterior fontanel was very protruding and distended, even when he sat up, the fontanel resembling the head of a cap mushroom on the cranial surface. The neck was flexible, and there was no neurological anomaly. The fundus oculi was normal, and the ear examination revealed no abnormality. The lumbar puncture showed a clear fluid, with 1.4 cells per cubic millimeter and 25 mg. of albumin per 100 cc.

The next day the child seemed to have recovered; the fontanel was rather depressed, but one could notice edema at the point of lumbar puncture, proving the persistence of a subcutaneous flow of the spinal fluid. The condition had returned to normal on July 10.

The history showed that on the morning of July 7 the infant had drunk in his bottle the contents of an ampule which had contained a large amount of vitamins A and D.

Case 2.—I. Jean-Louis, aged 7½ months, on Sept. 27 presented cerebral vomiting at 1 and 4 p. m., soon after having drunk his feeding. During the afternoon he was very sleepy, but at night he played and smiled normally.

On Sept. 28 this child, of 7,000 gm., presented a very prominent bulge of the fontanel, more conspicuous when he cried and without any pathological sign.

The lumbar puncture showed a clear fluid containing 1.8 cells per cubic millimeter, and 15 mg. of albumin, 80 mg. of sugar, and 730 mg. of chlorides per 100 cc.

The day ended well, and the next day the child had recovered completely.

Investigations showed that the child had taken an ampule containing the same large amount of vitamins A and D as in the preceding case.

Case 3.—M. Claudine, 3 months old, on Jan. 20 presented projectile vomiting 10 minutes after having drunk her feedings at 7 and 10 a. m. The child's father noticed that the fontanel was distended and protruding. In the afternoon she took her feedings but had a diarrheal stool. The temperature was normal.

On Jan. 21, the child vomited at 7 a. m., but she was gay, had good color, and was smiling. The fontanel was easily seen, protruding and tense. There was no meningeal or neurological sign. The blood pressure was 85/40. The lumbar pressure, measured with Claude's manometer in the lateral position, was 31 cm. of water; after jugular pressure it increased to 42 cm., and on abdominal pressure, to 56 cm. of water.

The spinal fluid was clear and contained 2.2 cells per cubic millimeter and 35 mg. of albumin, 60 mg. of glucose, and 760 mg. of chloride per 100 cc.

On the night of Jan. 21 the fontanel was still a little distended and prominent, but the child retained her feedings. The next day there was no disturbance.

The child had never been ill, except for a slight cold the previous week. On Jan. 19, at 7 p. m., she took with her feeding the contents of an ampule of the same composition as those ingested by the other two children, the three ampules coming from the same pharmaceutical laboratory.

Claudine retained this feeding and the following one, and it was 12 hours later that the first prominent vomiting occurred.

These three children had all received 12 to 24 hours before the disorders an ampule of Vitadone Forte, containing 350,000 units of vitamin A and 7.5 mg. of vitamin D_3 (calciferol), that is, 300,000 units.

We managed to reproduce the same syndrome in two hospitalized infants, 4 and 7 months old, after ingestion of this same drug. We also observed an acute hydrocephalus produced by hypervitaminosis A in a 2-month-old infant who received nose drops containing 50,000 units of vitamin A, supplemented with vitamin D. The summary of the case follows.

Case 4.—R. Alain, aged 2 months, weighing 4,700 gm., presented on Oct. 20, 1950, a prominent bulge of the fontanel, without any vomiting, discomfort, or increased temperature. The lumbar puncture showed a clear fluid containing 2.8 cells per cubic millimeter and 25 mg. of albumin per 100 cc.

On Oct. 24, the child seemed cured.

Four weeks previously he had had a slight rhinopharyngitis, which was initially treated with a product containing penicillin. During the preceding week, he had been given nose drops of a preparation containing 50,000 units of vitamin A per gram and vitamin D. The child received 3 drops in each nostril, i. e., 6 drops four times daily, which amounts to about 1 gm. This totaled in six days a large quantity, of approximately 300,000 units, similar to the dose received by our other patients.

The fact is known that the pituitary mucosa is an excellent way of absorption for certain drugs, not excluding the possibility that a certain amount of the oily substance instilled in the nostrils might have been swallowed, penetrating the gastric passage.

II. ACUTE HYPERVITAMINOSIS A IN THE INFANT

In the previous cases, the role of vitamin A seems significant to us. Excess of vitamin D, well known from the works of Professor Debré and his collaborators, Thiefry and Brissaud, produces quite different effects. Nevertheless, the addition of vitamin D, even in very small quantity, to vitamin A, as it occurred in our preceding case, does not necessarily validate our observation.

We have therefore studied the result of administration of plain vitamin A to the infant, and in three cases out of six we managed to reproduce the acute hydrocephalus.

We shall report only one of these cases here.

Case 5.—C. Joel, 4 months, was treated in our service beginning Dec. 12, 1951, for purulent staphylococcal pleuritis, which was cured, but he presented a periscissural softening, his fontanel was wide and normally tense.

On March 5, at 5 p. m., the child ingested an ampule containing 350,000 units of natural vitamin A.

On March 6, at 6 a. m., the nurse that fed him, who was not aware of the ingestion of the drug, noticed that the fontanel was bulging and formed a knob on the child's head; the child vomited after he drank. At 8 a. m. the bulging was considerable; there was no meningeal sign. On March 7, the fontanel was still a little tense. On March 8, all abnormalities had disappeared.

The child vomited only once, but, although the child's weight increased regularly, there was a slight loss of weight on March 6 and 7.*

Vitamin A alone, given orally and in very great dosage, is therefore the cause of this unexpected and transitory incident.

In our subsequent studies, we continued to use plain vitamin A, and we systematically observed the status of the fontanel, the cerebrospinal fluid pressure, the fundus oculi, and, especially, the blood vitamin A level. Several times we reproduced the same disturbances in infants, from the age of 24 days to 15 months.

The precise clinical study of six infants who presented disorders after ingestion of a single dose of 350,000 units of vitamin A induces us to describe a special syndrome characterized by the signs to be noted.

1. *Functional Disorders.*—We noticed 12 to 24 hours after the ingestion, almost always, repeated projectile vomiting, twice, cerebral vomiting and diarrhea, and

* With other infants, we proceeded exactly in the same way, but using synthetic vitamin A instead of the natural vitamin; yet we could not reproduce the syndrome. Neither could we reproduce it with subcutaneous injections of natural vitamin A (60,000 to 90,000 units).

usually, restlessness, discomfort, insomnia, or drowsiness. Four infants showed a rise in temperature to 102.2 F. (39 C.); most of them did not gain weight for 48 hours; one of them even lost weight.

The disorders were, however, not proportional to the severity of the hydrocephalus; they perhaps were even inversely proportional; in fact, the child whose fontanel was most bulging had no disorder whatsoever.

2. *Clinical Study.*—We insist on the isolated character of the distended fontanel, which in the most typical cases produces a proper mushroom-like protuberance on the child's head, but there is no meningeal sign or any neurological anomaly. The blood pressure is not modified.

We have systematically studied the cerebrospinal fluid, and it appeared chemically and cytologically normal. The study of the spinal fluid tension was more interesting. Measured with Claude's manometer, the child being in lateral position and not crying, the fluid tension showed values from 15 to 23 cm. of water, and from 22 to 30 cm. after jugular pressure. In another group of infants, not receiving vitamin A, we found under the same conditions the following values: 11 to 13 cm., and 22 to 23 cm. after jugular pressure.

This slight hypertension of the spinal fluid is not proportionate to the height of the tension of the fontanel, but after evacuation of a certain amount of fluid there is a marked reduction of the bulge.

In these six infants, we systematically studied the fundus oculi and the electroencephalogram, without noticing any alteration. Likewise, there was no modification of the prothrombin rate.

3. *Chemical Study.*—Much more interesting was the measure of plasma vitamin A absorption rate, which we studied through Carr and Price's color test.†

For infants of less than one year, the level was, on an empty stomach, from 75 to 132 I. U., the average for six children being 102 I. U. In opposition to Mr. H. Aron's statements, the individual variations seemed to us to be proportionate to the alimentary diet and to the drugs taken by the children. In fact, the highest level (132 I. U.), was observed in a case of cured rickets.

Six hours after ingestion of the drug, the values reached 400 to 714 I. U.; the average value for the six children was 513 I. U. The increase seemed proportionate to the values at the start and reached five times that value. A few exceptions, however, were noticed, and they certainly pertained to different individual capacities of absorption and assimilation.

Twelve hours later, the values fell to about 170 and 353 I. U., that is, to two to three times the value at the start. It should be noticed that the most bulging fontanels are not accompanied by the highest values.

In a second series of six children, of less than 2 years of age, but whose fontanels were closed, the values at the start were 110 to 170 I. U., or an average of 140 I. U.

Six hours after ingestion, they reached 308 to 1,060 I. U., or an average of 690 I. U., i. e., five times the initial value. Twelve hours later, they dropped to values between 160 and 297 I. U.

Altogether, these values were higher than those of the infants.

We can add that we never found vitamin A in the cerebrospinal fluid.

† Miss Larrue and Mr. Chaix assisted with this test.

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Acute hydrocephalus is, therefore, certainly produced by oral ingestion and absorption of a large amount of vitamin A. This is in connection with an excessive secretion of cerebrospinal fluid, evidenced by the increase of cerebrospinal fluid pressure. The hydrocephalus develops in parallel with the increase of vitamin A, but with a few hours' delay.

The connection between the spinal fluid and the vitamin A absorption rate are well known from studies by the veterinarians.[6] But, to our great surprise, it is hypovitaminosis which accompanies an excess of cerebrospinal fluid pressure. This fact seems so consistent that Canadian veterinarians rely on an increase of the spinal fluid pressure to reveal a hypovitaminosis A, and to treat it in time, in certain breeds of calves.

We succeeded in reproducing the syndrome of acute hydrocephalus ‡ in puppies from 3 to 4 months old.

One of them, weighing 4,000 gm., received an ampule of 350,000 units of vitamin A by mouth. It showed a very distinct tension of the fontanel. The initial level of plasma vitamin A was 310 I. U.; 6 hours later it was 1,700 I. U.; 12 hours later it fell to 850 I. U.

Two other puppies took only the oily solvent (vitamin A destroyed); they showed no modification.

Two other puppies received during three days 100,000 units of vitamin A a day, and they showed no disorder.

In the dog, as in the human being, vitamin A produces an acute and transitory hydrocephalus, provided one gets a massive and rapid absorption, expressed by an important increase in plasma vitamin.

SUMMARY

Our clinical observations and our work on infants and animals convinces us that the acute hydrocephalus, with intensive bulge of the fontanel, produced by the rapid absorption of vitamin A is a transitory and harmless disorder in both its immediate and its remote prognosis.

It seems to us, however, quite harmful to use this treatment in such excessive dosage. On our request, this drug is now being prepared in the concentration of 70,000 units of vitamin A and 2 mg. of vitamin D, and in this dosage it has thus far been perfectly tolerated.

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Vitamin A Poisoning in Adults*

With Description of a Case

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THE present report concerns an adult with long standing vitamin A poisoning who had the highest fasting blood vitamin A ...el ever recorded. During the course of her ...oxication, which lasted eight and one-half ...rs, she was hospitalized ten times. Before the ...rrect diagnosis of hypervitaminosis A was ...ablished the following diagnoses had been ...nsidered: brain tumor, serous meningitis for ...hich she underwent a subtemporal decompres..., cirotic encephalitis, viral radiculoen...phalitis, psychoneurosis and generalized in...ctious arthritis. For the first time x-ray evidence ...bone involvement in an adult is described.

HISTORICAL

As early as 1857 acute illness had been ...scribed by aretic explorers following the in...stion of polar bear liver. Elisha Kane men...oned "vertigo, diarrhea, and their concomit...nts" as the aftermath of eating this food.[1] ...ckson[2] in 1899 mentioned that many arctic ...plorers of that period knew of the poisonous ...alities of polar bear liver. It was not until ...942, however, that the toxic substance in polar ...ar liver was identified by Rodahl and Moore[3] ...being vitamin A.

The first reports of toxic effects of excess ...tamin A in animals appeared in the late 1920's ...nd early 1930's. von Drigalski administered a ...tamin concentrate rich in vitamin A to white ...ts.[4] In four to six days these animals showed ...shevelled fur and marked emaciation. After ...ve to eight days conjunctivitis, hemorrhagic ...initis and diarrhea appeared. Within five to ...ineteen days the animals died. Collazo and ...drigues conducted similar experiments.[5] They ...ted inflammatory changes of the eyes, bilateral exophthalmos, cessation of growth and spontaneous fracture of bones in addition to trophic changes of the skin ...nd loss of hair. When the overdosage was stopped, the animals recovered and gained weight. Russo was unable to duplicate these effects in animals and concluded that high doses of vitamin A were not toxic.[6] Clausen in an excellent review of the experimental work on this subject came to the conclusion that "the literature was so contradictory at that time (1938) so as to afford no evidence that vitamin A would have a harmful effect on human beings."[7] Subsequently, Moore and Wang[8] produced fatal uterine hemorrhage in adult pregnant rats by the administration of toxic doses of vitamin A.

In 1912 Czerny administered large doses of cod liver oil to tuberculous children and observed the development of seborrheic dermatitis of the face and scalp.[9] Getz and his associates administered 50 cc. of halibut liver oil (2,000,000 units of vitamin A) in a single dose to four adults.[10] All experienced dull headaches but no other symptoms. Rodahl and Moore cite the instance of a man who consumed 6,000,000 units of vitamin A daily for five days at which time he became severely ill, complaining mainly of dizziness. On stopping the vitamin A he rapidly recovered and appeared to be normal within ten days. Clinical recognition of chronic vitamin A poisoning was first described in a child by Josephs in 1944.[11] Since then other reports have appeared, mainly in pediatric literature. By 1952 Caffey had listed twenty-two reported cases in children.[12] Only two cases of chronic hypervitaminosis A have been reported in adults, neither of whom exhibited the advanced changes present in our patient.[13,14]

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CLINICAL CLASSIFICATION

A clinical classification suggested by Knudson and Rothman divides hypervitaminosis A into acute and chronic forms as they exist in infants and adults.[10]

Acute Hypervitaminosis A in Infants. Acute hypervitaminosis A in infants resulting from accidental ingestion of large doses of vitamin A has been reported by Maric and See, by Mulloy and by Garcia.[10–12] In addition to vomiting and drowsiness, there was marked bulging of the fontanelle in every case. During their illness there were no evidences of cervical rigidity, abnormal neurologic signs or fever. In every instance recovery was rapid and complete following lumbar puncture and abstinence from vitamin A. In Mulloy's case the anterior fontanelle bulged 2 cm. The spinal fluid was under greatly increased pressure and contained 30 cells of which 98 per cent were lymphocytes. The Pandy test was slightly positive and no bacterial growth was obtained. The serum vitamin A level on admission was 715 units, and after four days without vitamins fell to 217 units.* A fine cutaneous desquamation developed over the trunk and extremities after a few days.

Acute Hypervitaminosis A in Adults. Symptoms of acute hypervitaminosis A in adults appear within four to eight hours following ingestion of toxic doses of vitamin A. Headache is the predominant manifestation and has been described as being violent and localized in the forehead and eyes. Nausea, vomiting, vertigo, drowziness, irritability and localized or generalized peeling of the skin are common findings. Lonie reported a family with vitamin A poisoning following a meal of shark liver.[10] Their symptoms consisted of severe headache, dizziness, nausea and vomiting. Recovery was rapid and complete. Within thirty-six hours desquamation of the skin started and later became extensive.

Chronic Hypervitaminosis A in Infants. In 1944 Josephs reported the first case of chronic hypervitaminosis A in a child.[11] Toomey and Morissette in 1947 described a similar case.[10] They were able to reproduce the original symptoms and signs in this two year old infant by giving 6,200,000 units of vitamin A during a period of fourteen days. Gribetz, Silverman and Sobel[13] reviewed the literature and summarized the findings in seventeen cases, including two cases of their own. Most instances occurred in the second or third year of life and followed months of excessive vitamin A intake. The most prominent features were cortical thickening of the bones, painful swellings in the extremities, irritability, pruritus, hepatomegaly, limitation of motion or inability to stand, sparse coarse hair, fissuring of the lips, constipation and a failure to gain weight. Splenomegaly was noted only by Josephs.

Gribetz et al. reported the case of a seventeen month infant who had enlargement of the head. Slightly dilated ventricles on pneumoencephalogram and ventriculogram suggested hydrocephalus. Following a reduction in vitamin A intake her head assumed normal proportions. A six and one-half month old girl with chronic hypervitaminosis A was described by Arena as having marked craniotabes.[14] X-ray of the skull showed uniformly thin bones. There was no hyperostosis. After elimination of all vitamin preparations the skull bones became normal.

Chronic Hypervitaminosis A in Adults. Only two cases of chronic hypervitaminosis A have been reported in adults. Sulzberger and Lazar in 1951 described a forty-four year old woman who, in an attempt to prevent "colds," had taken 600,000 units of vitamin A daily for eighteen months, supplemented by occasional doses of 1 to 2 million units.[15] Her complaints and findings included the following: menstrual periods of shorter duration and decreased flow; generalized joint and bone pains; soreness and fissuring at the corners of the mouth and nasal apertures; dry rough skin with brawny desquamation, peculiar pigmentation, excessive loss of hair, and generalized pruritus; night sweats; and increased prominence of the eyes. Note should be made that x-rays of several long bones and joints revealed normal features, and that headaches were not included as part of the symptomatology. Her highest vitamin A level was 60 blue units.*

Bifulco[16] in 1953 presented the case of a fifty-two year old woman with a four-year history of daily intake of 100,000 units of vitamin A. After one year on this regimen insomnia and listlessness appeared. Subsequently, loss of hair, stiffness and pain in the joints, a patch of pigmentation on the forehead, and increased prominence of the eyes were noted. Because of possible dental infection, teeth were extracted with resultant severe hemorrhage. Anorexia, marked loss of weight and spontaneous oozing of blood from the nose appeared. Menses, which had become irregular about one year after the onset of vitamin

* 1 mg. of vitamin A = 3.33 U. S. P. units.

* Normal = 10 to 20 blue units.

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...A ingestion, ceased within the following two ... years. The eyes were prominent and pulsated, ...and the fundi disclosed abnormal pulsation of ...ne retinal veins. A thumping headache devel... ...ped one month prior to the cessation of vitamin ...n ingestion and was still present six months after ...il vitamin A had been stopped. Cerebral ...ngiography was performed but failed to dis... ...ose an aneurysm. There was pain on flexion of ...il joints and marked tenderness was elicited ...ver the long bones of the extremities. There was ...o joint swelling or deformity. No mention was ...made of x-rays. Headache and pulsation of the ...ght eye persisted at the time of the report, all ...ther manifestations having returned to normal ...veral weeks after vitamin A was stopped.

CASE REPORT

S. L., a twenty-one year old unmarried white ...male was admitted on July 24, 1945, to hospi... ...l "A." Her chief complaints were diplopia for ...ve weeks and headaches and nausea for four ...eeks. Five weeks prior to admission she noted ...urring of vision followed by diplopia. This ...rsisted and was in turn followed by severe ...ontal headaches and nausea. Three weeks prior ... admission the patient began to have incon... ...pence of urine and nocturia, as well as oc... ...sional enuresis. She also developed urgency ...d frequency but no burning on urination. ...stemic review revealed occasional joint pains ...curring with inclement weather. She had a ...d for two weeks, and a cough for one week ...or to admission. Her family history revealed ...pertension in two grandparents and cancer in ...hird. Menses began at twelve years with ...ular thirty-day cycles lasting five days with a ...mal flow. There was occasional dysmenor... ...h. She smoked one pack of cigarettes a day. ...he physical examination at this time showed ...perature 99.6°F., pulse 84, respirations 20, ...d pressure 105/75. She was a well developed, ... nourished white female in no distress. The ... reacted equally to accommodation and ... Pupils were round, the left slightly larger ... the right. There was internal strabismus ... uncrossed diplopia and nystagmoid twitch... ...in both lateral gazes, right more than left. ... repeated lateral eye movements the nys... ...us became more sustained. Fundus exam... ...on showed both discs hyperemic, margins ...ly blurred, slight venous congestion and a ...hemorrhage near the right disc nasally. ...conduction was greater than air conduction on the left. Facial sensations, corneal reflexes and jaw motion were normal. Hearing was normal. Tongue movements, swallowing and taste were normal. The neck was supple and no glands were palpable. The lungs were clear to percussion and auscultation. Examination of the heart showed regular sinus rhythm, P_2 greater than A_2, the point of maximal impulse in the fifth intercostal space. There were no thrills or murmurs. The liver, spleen and kidneys were not felt and no abdominal tenderness was present. No costovertebral angle tenderness or vertebral tenderness was elicited. Motor power was normal in all limbs. The reflexes were symmetrical and equal throughout except for the right knee jerk which was greater than the left. No pathologic reflexes were elicited. The finger to nose, heel to knee and pronation-supination tests were normal. Light touch and pinprick were normal throughout. Position and vibration were appreciated in the great toes; however, vibration was diminished generally on the left. Gait and speech were unimpaired. The patient was alert, intelligent and cooperative.

X-ray of the skull showed some increase in the digital markings of the cranial vault. The sella turcica was normal in size and shape. No abnormal calcifications were demonstrated. Examination of the skull following direct ventricular injection of air showed that the anterior horns were well outlined. They showed some dilatation but no evidence of a shift. The bodies of both lateral ventricles, however, were poorly outlined. The posterior and inferior horns appeared normal. The visual fields on two separate occasions showed a small but definite constriction bilaterally, the left slightly more than the right. Visual acuity was O.D. 10/15, O.S. 10/10.

The laboratory findings were as follows: urinalysis, 1 plus albumin on 2 occasions; red blood count 4,000,000; hemoglobin 81 per cent; white blood count 10,700, with a normal differential count: E.S.R. 3 mm./one hour; spinal fluid, glucose 56 mg. per cent, total protein 31 mg. per cent; ventricular fluid from the right side, total protein 15.6 mg. per cent; serologic tests for syphilis negative in blood and spinal fluid.

During the patient's stay a definite increase in the degree of choked disc was noted, more papilledema being present on the right than on the left. When she looked to the right the nystagmus was definite and well sustained, the right

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lateral deviation being greater than on the left. The patient also began to notice diplopia on straight gaze. On occasion she complained of pain in her left trapezius region and left leg. Ventriculography was done, both anterior ventricles being tapped. A moderate amount of clear colorless fluid escaped under increased pressure from the right anterior horn. When the head was tilted no additional fluid was obtained from the right anterior horn and therefore the left anterior horn was entered. Although air had been injected into the right anterior horn under increased pressure, no air bubbles appeared in the brain cannula when the left anterior horn was tapped and the fluid which escaped seemed to be slightly cloudy. Ventriculograms revealed the lateral ventricles to be normal in shape, size and position. The third and fourth ventricles were not well visualized. An electrocephalogram suggested posterior fossa tumor or some other subtentorial disturbance.

The patient left the hospital on September 6, 1945, with a diagnosis of intracranial neoplasm. Six days later she was admitted to hospital "B." At this institution additional history was obtained. The patient stated that she had "ichthyosis" as long as she could remember and had been taking large doses of vitamin A for the past one and one-half years with remarkable improvement of the skin. Otherwise both history and physical examination were unchanged. X-ray of the skull confirmed the impression of increased intracranial pressure. Because of the normal lateral ventricles the neurosurgeon believed that poor visualization of the third and fourth ventricles was not due to obstruction at the foramen of Monro, aqueduct of Sylvius or the fourth ventricle. He favored a diagnosis of serous meningitis and performed a right subtemporal decompression. There was a continued outpouring of fluid after the dura was incised.

She was readmitted to hospital "B" on August 15, 1946, approximately eleven months after her previous discharge. She had remained "relatively well" until six weeks before this admission, when she began to have pain in the region of the seventh right rib in the anterior axillary line. This pain seemed to spread posteriorly to the region of the ninth thoracic vertebra and later also to the right ninth costochondral junction. At times she noticed that her legs began to feel heavy. Three days before admission she noticed numbness in the saddle area. Her right-sided chest pain was accentuated by coughing and sneezing but not by straining. It was also increased if the patient lay on her abdomen.

Physical examination at this time revealed a markedly bulging area at the site of the previous subtemporal decompression. The neck was quite supple but extreme flexion caused the patient's chest pain to appear. Although the fundi showed rather full veins, the discs were well outlined. There was some diplopia on left lateral gaze and some left central facial weakness. Sensory and motor findings were normal. Reflexes were active and equal except for some hyperactivity of the biceps jerk on the left. Hoffmann's sign was positive bilaterally. There was localized tenderness over the lower chest wall at about the ninth right rib anteriorly. No spine tenderness was elicited.

Studies at this time showed the urine and the blood count to be normal. The urea clearance test and the blood sugar, urea nitrogen, total protein and cholesterol were within normal limits. The cephalin flocculation and thymol turbidity tests were normal. A lumbar puncture revealed clear fluid under normal pressure with a negative Pandy test. X-ray of the chest failed to reveal any local pathologic condition of the bone. The x-ray of the spine showed some hypertrophic lipping of the contiguous surfaces of the fifth and sixth thoracic vertebrae. Skull x-rays were normal except for the bony defect of the previous decompression. A pneumoencephalogram was likewise normal. Intravenous pyelography showed no abnormality.

During her hospitalization of two and one-half months there was no improvement. She was treated with thiamin chloride for possible intercostal neuritis. Radiation therapy also failed to cause any lessening of her pain. The medical consultant believed that her pain was probably unrelated to her cerebral lesion. The neurologist suggested that such pain is often the result of medulloblastoma metastases, although in this case a large psychic element had to be considered. There was no improvement and the patient was discharged with the diagnosis of costalgia, cause unknown.

The patient was admitted to hospital "C" on February 10, 1947, because of persistence of her complaints. Examination revealed a markedly bulging right subtemporal decompression. The fundi showed pallor and the disc margins were somewhat indistinct. There appeared to be atrophy of the right rhomboid and supra-

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scapular muscles. The right scapula was winged. The patient stood in a position of forward flexion and because of pain in the right hip and knee favored the right lower extremity in walking. Blood studies included a serum phosphorus of 4.0 mg. and alkaline phosphatase of 6.2 units.

X-rays of the chest, dorsal spine and foramen magnum were considered normal. Fever therapy with typhoid vaccine was given but the results, while definite, were far from dramatic. A tantalum cranioplasty was performed and the patient was discharged on April 7, 1947. The discharge diagnosis was chronic encephalitis.

One month later the patient was admitted to hospital "D" with a febrile illness of eight days' duration during which period the pains in her knees, elbows, right hip and left shoulder had become aggravated. The exact nature of this acute illness was never determined. While physical examination of the chest was always negative, indefinite findings on lung x-ray suggested a pneumonitis. Many tests and observations were made during this hospitalization, the most significant of which were: sparse eyebrows, pigmentation over the skin of the abdomen, hepatosplenomegaly, moderate anemia and marked tilting of the pelvis. Tests for liver function were normal, including BSP and hippuric acid excretion tests.

During this hospitalization her bone and joint pains continued and her deformity seemed more marked. It was noted that while the pain in her back persisted, she was comfortable when perfectly quiet. Her greatest difficulty occurred with change in position after a period of rest. The back muscles showed spasm of moderate degree and there was a flexion contracture of the right hip. The hip joint was entirely normal, motion in all directions being free and painless, with no tenderness present. Moderate tenderness was noted in the right iliolumbar angle, with negligible tenderness of the spine and sacroiliac joints. A plaster of Paris spica was applied from the nipple line to the middle of the right leg. On July 14, 1947, she was discharged. When she returned five weeks later for removal of the cast there was no apparent improvement. At this time the liver was felt one and one-half fingerbreadths below the costal margin. The skin was uniformly hyperpigmented, dry and shiny. The palms were cracked and scaling. One neurologist believed that the picture was one of dorsal and posterior root disorder, at various levels affecting the thoracic and lumbosacral segments. He believed that the hepatosplenomegaly had a common etiology with that of the neuropathology and therefore diagnosed encephalomyeloradiculitis due to a virus infection.

The patient re-entered hospital "D" for the third time in five months because physiotherapy, which had been started during her previous admission and continued while at home, failed to arrest the progress of her disease or alleviate her symptoms. It was noted that she had continued to take 500,000 units of vitamin A daily for her skin condition and this was continuously administered during her hospital stay. Right lateral rotatory nystagmus was present. The lips showed desquamation, and the pigmented skin was noted to be most prominent over the left mid-abdomen. Tests for Addison's disease were negative. Biopsy of the skin did not show hemosiderin deposits. The basal metabolic rate was minus 1 per cent. Special oblique studies of the lumbar vertebrae showed no abnormality, although she now had a completely rigid "poker" spine. A plaster jacket was applied from the groin to the axilla with considerable relief. At the time of discharge on November 11, 1947, she still had a two-fingerbreadth enlargement of the liver.

Five months later, April 6, 1948, she had a muscle biopsy at hospital "E." Microscopic sections failed to reveal lymphoid infiltration. The following month she was readmitted because of multiple severe joint pains and inability to walk straight. The physical examination showed diplopia on lateral gaze, limited chest expansion, drooping right shoulder, elevated right hip, shuffling gait, bilateral hip limp, rigid back, generally limited joint motion, trunk inclined forward and flexion contractures of the knees and hips. X-ray studies were read as showing incomplete fusion of the bodies of the fourth and fifth cervical vertebrae, an ankylosing process of the upper dorsal spine, a slight list of the lumbar spine to the left without evidence of an arthritic process, and moderate arthritic changes in both sacroiliac joints.

The following were described as radiographically normal: chest, right shoulder girdle, both hips and right knee. Laboratory studies revealed an elevated sedimentation rate and increased blood alkaline phosphatase. The patient was treated with orthopedic measures and discharged to the outpatient department for continued physiotherapy. The discharge diagnoses were

1A 1B

FIG. 1. A and B, patient at time of admission. Note bulge in right temporal area.

Marie-Strümpell arthritis and generalized infectious arthritis.

During the next five-year period she was treated by chiropractic and osteopathic methods with no improvement in her status. Bone pains had increased and disability was more marked. She continued the use of vitamin A in doses of 500,000 units daily.

She first came under our care on February 5, 1953. We were aware of reports dealing with the toxic effects of vitamin A and suspected that our patient's illness could be on this basis. Accordingly, blood was drawn and examined for vitamin A content. When this was found to be unusually high, hospitalization was advised.

She was admitted to the Jewish Hospital of Brooklyn on February 12, 1953, because of progression of the complaints for which she had been previously hospitalized. In the past five years she had lost 20 pounds as a result of anorexia, severe diffuse pruritus and inability to sleep because of pain.

Examination revealed an alert, cooperative, intelligent female in constant pain aggravated by any attempt to change her position. (Figs. 1A and B.) The blood pressure was 110/70, pulse 90 and respirations 18 per minute. The right subtemporal decompression was tense and bulged markedly. Her pupils were round, regular, equal in size, and reacted to light and accommodation. Neither diplopia nor nystagmus was present. The fundi were normal. The mucous membranes of the mouth were normal. Many teeth were missing but those remaining were normal. No adenopathy was present. The thyroid gland was not palpable. The breasts were normal. The lungs were clear to percussion and auscultation and the heart was normal. No abdominal masses or organs were palpable. Rectal examination was negative. The results of

neurologic examination were as follows: cranial nerves intact; cerebellar tests normal; sensory and motor systems intact; reflexes equal throughout except for the right knee jerk which was greater than the left; no pathologic reflexes. Dermatologic findings were: thinning of scalp hair, axillary hair and eyebrows; nails normal; skin diffusely pigmented, coarse over most of the body, but dry, shiny and somewhat atrophic with associated loss of lanugo hair over the arms and legs; elbows keratotic and scaly; palms and soles scaling, with deeply marked furrows and dried blebs; many scratch marks throughout. Orthopedic examination showed: temporomandibular joints and facial muscles normal; neck movements normal in range and strength; spine fixed in extension although tilted forward and slightly to the left, without tenderness but painful on motion; extreme paravertebral wasting; rib cage fixed and tender on compression; right shoulder painful on elevation to 90 degrees and fixed after 110 degrees; elbows, wrists and fingers normal; left hip relatively normal; right hip painful with limitation of terminal 30 degrees of extension and 50 degrees of abduction; the feet showed fixed hallus valgus.

Laboratory studies were as follows: hemoglobin 74 to 81 per cent (15 gm. = 100 per cent); red blood count 3.7 to 4.4 million; white blood count 6,400 to 7,400; polymorphonuclears 64 per cent, bands 1 per cent, lymphocytes 31 per cent, monocytes 2 per cent, eosinophils 1 per cent, basophils 1 per cent, platelets adequate; hematocrit 42 per cent. Bone marrow aspiration normal; myeloblasts 5 per cent, neutrophilic myelocytes 9 per cent, eosinophilic myelocytes 0, metamelocytes 38 per cent, staff forms 39 per cent, polymorphonuclears 6 per cent, eosinophils 3 per cent, megakaryocytes adequate, granulocyte:polymorph ratio 91:9; granulocyte:erythrocyte ratio 90:10; red cell sedimentation rate 22 mm./one hour; bleeding time two minutes; clotting time three minutes fifteen seconds; urinalysis, specific gravity 1.022, albumin 0, sugar 0, microscopic examination negative; basal metabolism, plus 12 and plus 10; electrocardiogram within normal limits. (See Table 1 for chemical determinations.)

The results of x-ray examination were as follows: Skull: right subtemporal decompression with tantalum plate *in situ;* slight thinning of vault of skull; slight hyperostosis frontalis interna. Shoulders: thinning of wings of scapulae, more marked on left; thin rim of calcification parallel to rim of glenoid fossa. Ribs: normal. Dorsal spine: narrowed intervertebral spaces with thinly calcified anterior spinal ligament; moderate decalcification of vertebral bodies; pedicles and laminae intact; interpedicular distances normal. Lumbar spine: straightened lordotic curve; moderate decalcification of vertebral bodies; intervertebral spaces normal; minimal spur formation at anterior aspects of

TABLE 1

BLOOD DETERMINATIONS

	February 13	March 3	April 14
Sugar*	100	96	73
Uric acid*	4.2	3.7	4.0
Icterus index	12	15	16
Ca*	9.6	12.0	11.5
Total protein, gm./100 cc.	9.4	9.3	8.9
Albumin/globulin ratio	7.3	.....	7.6
Vitamin C* (normal = .7–2.3)	1.6	.....	1.6
Bilirubin, free*	0.7	.....	.....
Bilirubin, total*	0.2	.....	.....
Total cholesterol*	0.7	.....	.....
% Free cholesterol	287	227	222
CO_2 combining power (vol. %)	32	28	28
Sodium*	61.6	60.9	56.0
Potassium*	331	322	318
Chloride*	16.3	16.1	15.9
Inorganic phosphorus*	328	342	362
Alkaline phosphatase†	3.8	3.4	4.1
Cephalin flocculation	3.3	3.6	3.7
Thymol turbidity	0	.....	.....
Amylase (wohlgemuth units)	4.4	.....	.....
Amylase control	90	.....	.....
Amino acid*	72	.....	.....
Total fatty acids*	7.4	.....	.....
Phospholipid phosphorus*	330	.....	.....
Total lipid (bloor method)*	10.5	10.4	.....
Prothrombin time	418	.....	.....
Prothrombin time control	14.4 sec.	14.0 sec.	.....
Protein-bound iodine µg./% (normal = 3–8)	10.1 sec.	11.2 sec.	.....
	.....	.....	1.8

Cleric Acid* (normal = 1.5–2.4)

Date	
2/23	1.9
2/24	1.9
2/25	1.8
2/26	1.7
2/27	1.7

Prothrombin consumption test: 40.6 sec.
Prothrombin consumption control: 43.4 sec.
Prothrombin Dilution Test:

100% Plasma	13.2 sec.
75% Plasma	16.8 sec.
50% Plasma	21.8 sec.
33% Plasma	30.5 sec.
16.5% Plasma	59.3 sec.

* Milligrams per 100 ml.
† Bodansky units.

URINE DETERMINATIONS
(*Twenty-four-hour Excretion*)

Calcium	736 mg./1,260 ml.	(Normal = 100–300 mg.)
Cleric acid	763 mg./total	(Normal = 200–1,200 mg.)
Phosphorus	914.5 mg./1,180 ml. 878 mg./1,260 ml. 652 mg./1,180 ml.	(Normal = 800–1,300 mg.)

2A 2B

FIG. 2. A, anteroposterior roentgenogram of lumbar spine. Note the calcification in the ligamenta flava (letters L overlying these structures between the third and fourth and fourth and fifth lumbar vertebrae). Similar changes exist in the ligamenta flava between the neural arches of the upper lumbar vertebrae. B, right posterior oblique roentgenogram of lumbar spine. The white arrows point to the calcified ligamenta flava. The black arrows indicate the loss of definition of the apophyseal joints, with narrowing of the joint spaces.

FIG. 3. Anteroposterior roentgenogram of pelvis. Periosteal elevation along ischial ramus (A), and calcification in articular capsule (B) are indicated by the respective black arrows.

upper lumbar vertebral bodies; apophyseal joints narrowed, with loss of definition of their articular surfaces; moderate calcification of ligamentum flavum; slight calcification of iliolumbar ligaments. (Figs. 2A and B.) Pelvis: sacroiliac joints normal; pelvic inlet distorted because of inability of patient to assume recumbent position; calcification in periosteal elevations and probable bone formation in lateral aspects of both iliac bones just above acetabular sockets; calcification in capsule of hip joint at insertion into superior rim of acetabulum bilaterally; similar but lesser degree of calcification in inferior aspects; shaggy appearance of ascending ramus of right ischium; a single spur-like projection of ascending ramus of left ischium and of lesser trochanter of right femur. (Fig 3.) Hands: normal. Feet: normal. Knees: calcification at anterior tibial tubercles and anterior inferior aspects of patellas bilaterally; local thickening at upper medial aspect of left tibia; bony densities not disturbed. (Fig. 4.) Os calcis: calcification at

insertion of achilles and plantar tendons bilaterally.

Skin biopsy from the mid-abdomen showed moderate hyperkeratosis with thickening of the granular layer which contained foci of dyskeratosis as evidenced by marked vacuolization of the cells; dense hyperpigmentation of the basal layer with intracellular melanin involving some of the overlying cells of the prickle layer; normal corium. The diagnosis was hyperkeratosis with pigmentation.

Bone biopsy from the right tibial tubercle showed broad osseous trabeculae which in places presented calcification of the cartilage, thickening of the periosteum and normal marrow spaces. (Fig. 5A and B.) The diagnosis was calcification in cartilaginous tissues with thickened periosteum.

Immediately after the patient was admitted to the hospital all vitamin A medication was stopped and she was given a normal hospital diet.* Within two and a half weeks her itching had disappeared and there were no further evidences of scratch marks. At the end of one month her skin texture had improved, her bone pains were markedly diminished, her appetite was excellent and she had gained weight. Six weeks after admission she woke one morning with marked dizziness and diplopia. There was no headache. Nystagmus was present on lateral gaze. The fundi were normal. Her diplopia gradually receded and was completely gone by the end of one week. Two months after vitamin A medication had been stopped, all spontaneous pain had gone and no further sedation was needed. Her posture had begun to improve.

During her stay she had three normal menstrual periods occurring at monthly intervals and lasting five days with a normal flow. Her improvement was continuous and she was discharged on April 26, 1953.

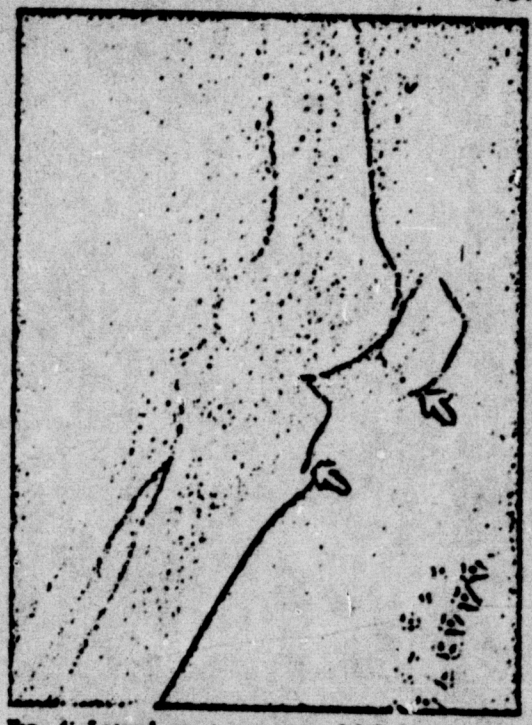

FIG. 4. Lateral roentgenogram of left knee. White arrows point to calcification in infrapatellar ligament.

COMMENT

Hypervitaminosis A may result from the ingestion of large amounts of vitamin A concentrates taken alone or in combination with other vitamins or minerals. Large doses of vitamin A are used in the treatment of skin, eye, renal, gynecologic and ear disorders as well as the common cold. The minimal daily requirement of vitamin A is 5,000 to 7,000 international units. In the usual diet this requirement is derived from both vitamin A and its precursor carotene, which is converted in the intestinal wall and possibly elsewhere, into vitamin A.[23–26] The conversion of carotene to vitamin A is limited and may not provide sufficient vitamin A to maintain the patient during stress.[26] Moreover, there is evidence to indicate that the conversion of carotene to vitamin A is impaired in some diseases, such as diabetes.[27–44]

Vitamin A is absorbed as the free alcohol and is esterified in the intestinal wall. Following vitamin A intake the rise in serum levels is due to the ester fraction, most of which is then deposited in the liver as such.[21,45] Vitamin A alcohol levels are not directly influenced by ingestion. The vitamin A alcohol level seems to be a measure of vitamin A storage.[46] In severe infection, in hepatocellular disease and in vitamin A depletion the plasma vitamin A alcohol level is usually low. The normal vitamin A blood level is 30 to 70 μg. and may rise to 1,000 to 2,000 μg. soon after the ingestion of very large doses of vitamin A. This is a temporary state and does not alter the subsequent fasting level.

The fasting level of 2,000 μg. per 100 cc. in our patient is the highest reported in man. Unlike such high levels observed following administra-

* 7,500 units of vitamin A daily.

5A 5B

FIG. 5. Right tibial tubercle biopsy. A, note the marked periosteal thickening; B, note the calcification in the cartilaginous tissue.

tions of vitamin A, most of the blood vitamin A content in this patient was in the form of the free alcohol, not as ester. This high percentage of vitamin A alcohol with high total blood levels of vitamin A has been observed in a child reported by one of us.[21] There is a possibility that not only the total vitamin A but the relatively high percentage of alcohol has significance in the diagnosis of hypervitaminosis A. In the previously reported adult cases the vitamin A level was 60 blue units* in one and unrecorded in the other.

The high vitamin A blood level of our patient was the result of continued daily ingestion of vitamin A for eight and one-half years. After four months of taking 25,000 units daily, she increased her dosage to 50,000 units and then rapidly to 500,000 units daily. On occasion, an additional dosage of 500,000 units was taken. The preparations of vitamin A which she had taken were stated by their manufacturers to be free of vitamin D.¶

During the course of this study, we had the opportunity of examining the blood of four other patients who had taken large doses of vitamin A over prolonged periods of time. While we cannot be certain that blood levels are a good index of vitamin A storage, they may be an index of toxicity since the transfer of vitamin A in the body is related to blood levels rather than to the total amounts of vitamin A stored. One patient had taken 25,000 units daily for three years, then 25,000 to 50,000 units for the next three years, and finally 50,000 to 100,000 for two years. Her fasting blood level was 120 μg. per 100 cc. Another patient who consumed between 25,000 and 50,000 units daily for six years had a fasting level of 88 μg. per 100 cc. A third patient took 25,000 units daily for six years and had a normal fasting level of 60 μg. per 100 cc. A fourth patient who took 50,000 units daily had a fasting level of 225 μg. per 100 cc. after eight months. Only the first and last patients had any complaints referable to possible vitamin A toxicity. Both had headaches which subsided soon after they stopped vitamin A therapy. It is apparent that individual factors

*Normal = 10 to 20 blue units.

greatly affect the size and duration of the dose that will produce toxic effects.

Daily vitamin A plasma levels were determined during the eleven weeks of hospitalization to observe changes in the blood levels while the patient was on a normal hospital diet. (Fig. 6.)

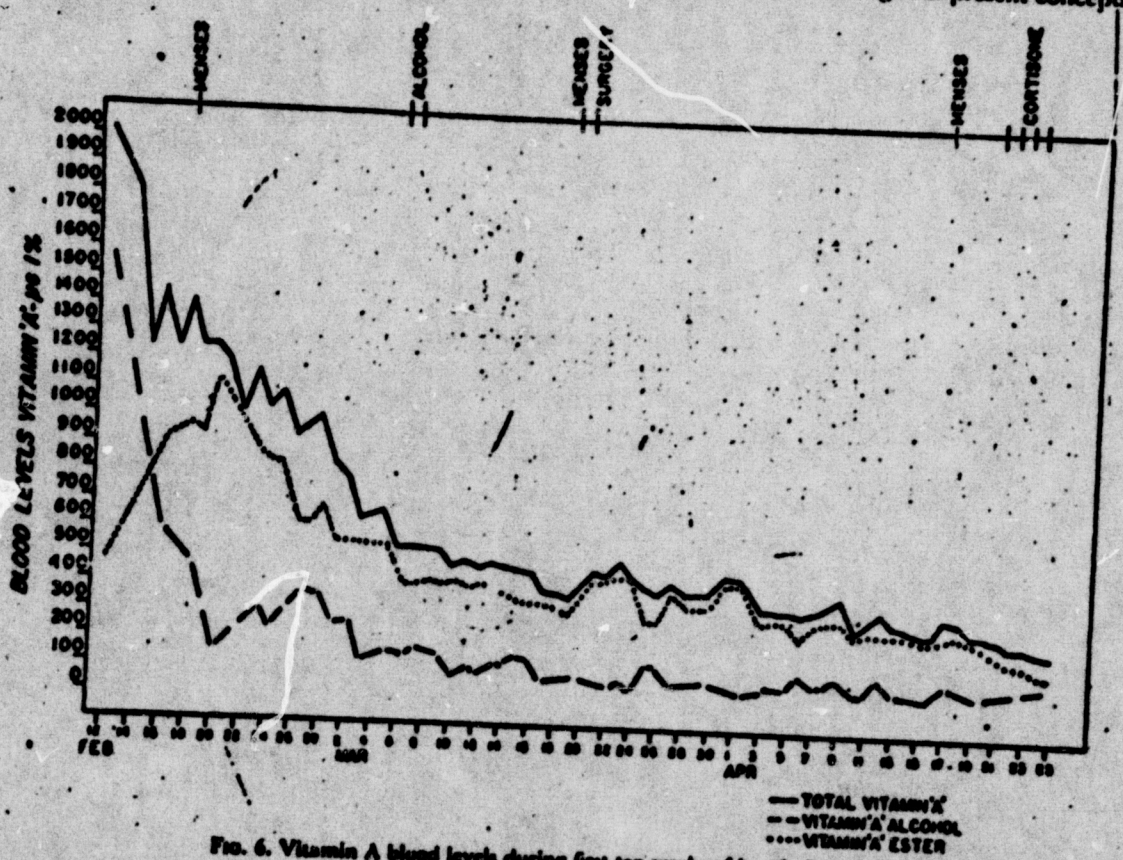

FIG. 6. Vitamin A blood levels during first ten weeks of hospitalization.

Vitamin A partitions into the alcohol and ester, together with the carotene level, were followed daily. Apart from the admission blood carotene level of 360 μg. per 100 cc., all carotene levels were between 180 and 290 μg. per 100 cc. (normal 54 to 310). At the onset the vitamin A levels, while extremely high, maintained the ratio of 20 per cent ester to 80 per cent alcohol. Immediately after stopping the vitamin A intake, there was a precipitous fall in the total vitamin A level, which reflected a parallel fall in the vitamin A alcohol. (Fig. 6.) However, during the first week while the alcohol fraction was falling, the ester fraction showed a very marked rise so that the ratio of ester to alcohol became reversed. This reversed ratio persisted.

We cannot establish from this study whether the alcohol, ester or total vitamin A level in the blood is the best measure of vitamin A storage, as we did not attempt to assay the liver or other tissues for vitamin A content. We are unable to explain the change in serum vitamin A alcohol-ester relationship in the light of present concepts of vitamin A metabolism. Is the vitamin A now being transported from the liver to the tissue in the form of ester? Has excess vitamin A in ester form been deposited in depots other than the liver, and is it now being released to the circulation in this esterified form? This would be consistent with the disappearance of hepatic enlargement. While the patient presented hepatomegaly during a six-month period, it was not present during the latter years of her illness in spite of continued excessive intake of vitamin A. This would not be expected if liver enlargement is considered an expression of vitamin A deposition. Repeated laboratory studies during her illness showed no evidence of impaired liver function, even when hepatomegaly was present. While liver enlargement has been found

frequently in children with vitamin A toxicity, it has not been noted in the previously reported adults. Splenomegaly, which was present in Josephs' case, was found in our case at one time.

Vitamin A tolerance tests carried out with half and full doses revealed no deviation from the normal. They showed the rise to be in the ester form while the alcohol fraction remained relatively unchanged.

Josephs[11,47] observed that a rise in serum lipids occurs early in the course of vitamin A toxicity, only to return to normal in spite of continued massive dosage. In our case the blood lipids were normal.

Alkaline phosphatase studies made while the patient was under our observation were repeatedly normal. However, six years before, elevated levels were found for a period of more than one year in two different hospitals. This finding is in agreement with the elevated levels found in many of the cases reported in children. This increase in serum alkaline phosphatase is probably associated with an increase in bone metabolism. In a previous adult case no alteration in the serum alkaline phosphatase was noted.

There has been interest in vitamin A as an agent in the prevention of renal calculi. In nephrolithiasis urinary citric acid tends to be low, and it has been observed that aqueous dispersions of vitamin A may cause a rise in the urinary citric acid level with possible resulting increased solubility of calcium stones.[46] We undertook studies of the blood levels and urinary excretion of citric acid, calcium and phosphorus. These blood findings were repeatedly within upper normal limits, as were the urinary excretion of citric acid and phosphorus, both in twenty-four-hour total output and concentration. However, the calcium excretion in the urine was markedly increased in both concentration and amount.

Rodahl[48] found that animals with experimental hypervitaminosis A showed low ascorbic acid serum levels and decreased amounts of ascorbic acid in the adrenals and liver. Moore and Wang[49] were unable to confirm this finding. Gribetz et al. did not find evidence of vitamin C deficiency in their studies and our patient had a normal vitamin C blood level. There were no clinical manifestations of scurvy.

Studies were made to determine the effects of menstruation, starvation, large amounts of alcohol, cortisone and operative procedures upon the total blood vitamin A levels as well as upon the alcohol and ester fractions.

It has been observed that normal women have a cyclic change in the serum vitamin A level which reaches a minimum at the time of menstruation and a maximum between menstrual periods.[50] This variation was not noted in our patient, who failed to show any appreciable change in relation to the menstrual cycle. The toxic levels exhibited by our patient could well have masked the slight changes noted in normal women with normal blood levels.

On two consecutive days the patient was given a pint of wine in addition to her regular diet. No influence on the vitamin A level was noted. Likewise, no appreciable effect was noticed after short periods of starvation. Because of the report that cortisone causes depletion in the amount of vitamin A present in the liver of the rat, our patient was given cortisone in doses of 300, 200, 100 and 100 mg. consecutively for four days.[51] No significant changes occurred in the vitamin A levels. This does not mean that the vitamin A stores were not affected. It would be of interest to observe the effect of cortisone in a patient presenting acute symptoms of hypervitaminosis A.

Biopsy of the tibial tubercle was performed under intravenous sodium pentothal anesthesia. There was a seventy-two-hour rise in the level of vitamin A from 350 μg. to a peak of 490 μg. This was due entirely to an increase in the ester fraction. During the following seventy-two hours the esters returned to their previous level. The alcohol fraction, which had remained unchanged throughout, rose markedly on the fifth and sixth postoperative days and then fell to the previous level. This vitamin A must have come from the body stores and it is interesting to note that the original rise was in the ester rather than in the alcohol fraction.

NEUROLOGIC CONSIDERATIONS

There is much evidence to indicate that vitamin A poisoning may produce intracranial disturbances.[15,16,18] In infants massive doses of vitamin A resulted in a marked increase in the cerebrospinal fluid pressure with bulging of the fontanelle. Cerebral manifestations such as severe headache, nausea, vomiting, dizziness, drowsiness and irritability are seen in adults

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who receive massive doses of vitamin A.[2,10,19] Both Gribetz and Arena have reported enlargement of the head in children with chronic hypervitaminosis A. In each instance there was a return to normal following withdrawal of vitamin A medication. In the case reported by Bifulco headaches played a prominent part. Since the headaches were associated with bilateral pulsating exophthalmos, Bifulco's patient was hospitalized for cerebral angiography which failed to disclose the suspected aneurysm. At the time of his report the exophthalmos had completely receded although pulsation of the right eye persisted. The exact nature of this mechanism is not apparent. However, the absence of an aneurysm, the recession of the exophthalmos, and the disappearance of the pulsation of the left eye since the withdrawal of vitamin A indicate a causal relationship.

In the case here reported the primary manifestations were headache, blurred vision, diplopia and nausea. These led to a diagnosis of serous meningitis, a condition of increased intracranial pressure considered to be due to thrombosis of the dural venous sinuses secondary to infection or, more rarely, trauma;[52] at times there has been no apparent etiology for the condition and Davidoff and Epstein[53] reported a series of cases which occurred mainly in young people with a history of infection of the middle ear or mastoid. When our patient was first seen by us the subtemporal decompression which had been done to relieve the suspected serous meningitis was still tense and bulging. Ten weeks after the excessive vitamin A intake was stopped, the decompression was completely soft. If she is to be considered to have had serous meningitis, vitamin A toxicity must be added to the causes of this condition. We have no knowledge as to whether dural vein thrombosis was present in this case but there is enough evidence to show that either excess production or decreased absorption of spinal fluid results from vitamin A toxicity. No other explanation can account for the persistence of a tense bulging decompression until vitamin A excess was stopped. The transient episode of diplopia and nystagmus that occurred during her hospital stay took place while her blood level was 344 μg. (more than seven times normal) and therefore while she was still experiencing vitamin A toxicity. The decompression has remained soft and no further cerebral manifestations have occurred since her discharge from the hospital.

SKELETAL MANIFESTATIONS

Our case is the only adult yet reported to demonstrate bone changes. Although bone pains and disability were present in both previously reported adult cases, no x-ray changes were noted in the one case in which they were sought. Radiologic findings in our patient were present in the dorsal and lumbar spine, pelvis, femora, patellae, tibiae, os calcii, scapulae and skull. The fundamental disorder consisted of calcification, with or without true bone formation, of the pericapsular, ligamentous, tendinous and subperiosteal structures. Also noted were decalcification in the skull, scapulae and vertebral bodies. The periosteal changes were the same as observed in the cases of hypervitaminosis A in children. The bone changes were far more extensive, however, probably due to the longer period of toxicity. Biopsy of the tibial tubercle of our patient showed thickened periosteum with secondary calcification. These findings are similar to those of Rineberg and Gross[54] whose biopsy of a child's fibula "showed a strip of newly formed, poorly calcified bone of coarse fibered structure such as is usually seen in ordinary productive periostitis." Six months after vitamin A intake was stopped the child's x-rays showed the subperiosteal calcification to have completely disappeared.

Except for those changes found in the spine of our patient, no similar alterations are demonstrated by any other disease. The spine changes had been diagnosed as Marie-Strümpell arthritis during a previous hospitalization elsewhere. In our opinion there are marked differences between the two conditions. In Marie-Strümpell arthritis the sacroiliac joints are usually involved early and progress with the disease; the anterior spinal ligaments show extensive calcification; there is progressive osteoporosis of the vertebral bodies; calcification of the ligamenta flavae is absent; and clinical improvement occurs slowly, if at all, with therapy.[55] On the other hand, in hypervitaminosis A we have noted that the sacroiliac joints are spared; that only minimal calcification of the anterior spinal ligament occurs; that there is only minimal decalcification of the vertebral bodies; that the ligamenta flavae are calcified; and probably most important, clinical improvement is marked and rapid upon the discontinuance of excessive vitamin A intake.

The marked decalcification of the scapulae

may be related to the high excretion of calcium in the urine. This in turn may be the result of hypervitaminosis A or inactivity.

Studies made in our patient at the time of discharge from the hospital revealed no radiologic improvement in spite of her marked clinical improvement. It is known that in children there is reversibility of the bone findings although these lag far behind the disappearance of symptoms. It is too early to know whether a similar return to normal will occur in our case.

The mechanisms that are responsible for the bone changes in our patient are uncertain. Wolbach[56] found acceleration of epiphyseal cartilage cell growth and maturation of the remodeling processes involved in bone growth in the course of his animal experimentation with hypervitaminosis A. There was accelerated periosteal bone formation in some areas whereas in others there was accelerated resorption of bone with osteoclasis. He found no cause for these changes in the parathyroids, thyroids, adrenals or pituitaries of his animals and concluded that the changes were probably due to a local vitamin A effect. Fell and McIlanby[57] subsequently demonstrated by means of tissue culture that the changes in bone were a direct effect of vitamin A locally. In our case the high blood level of vitamin A would favor the transportation of larger amounts of vitamin A than would otherwise occur.

DERMATOLOGIC MANIFESTATIONS

Dermatologic reactions to excessive intake of vitamin A have been reported consistently in both the acute and chronic states. Polar explorers who ate bear liver had peeling of the skin as early as two days after the high vitamin A repast. Associated with other symptoms and signs of toxicity in animals were skin lesions which ranged from disheveled fur to alopecia, seborrhea, exfoliation, hemorrhagic dermatoses and dry, cracked mucous membranes.

In the chronic intoxication of humans, pruritus is an early and often severe symptom. Fissuring and soreness at the corners of the mouth may appear and disappear in spite of continued use of vitamin A. Coarsening of the skin and alopecia are reported by almost all observers. Loss of the fine lanugo hairs of the extremities is also occasionally noted. Pigmentation of localized areas of skin was noted first by Sulzberger and again by Bifulco. In our patient pigmentation of some areas of skin was so marked that Addison's disease had been considered.

Our patient had suffered all of the skin manifestations cited during the prolonged course of her illness. Because disease of the skin was the initial reason for vitamin A therapy, the changes that took place during the course of toxicity were overlooked. Pruritus and thick, scaling, cracking palmar skin were the most distressing dermatologic manifestations of vitamin A toxicity.

The mechanisms responsible for the skin manifestations are far from clear. As to the pigmentation in our patient, we believe that it was probably secondary to the continued trauma of severe pruritus. The pigmentation was most marked over the abdomen and back where scratch marks were most evident during the early days of her last hospitalization. Biopsy of the skin of the abdomen showed hyperkeratosis and marked pigmentation.

Sulzberger considered hypovitaminosis A and hypothyroidism in the differential diagnosis because of the similarity of their dermatologic findings to those of hypervitaminosis A. That a definite antagonism exists between vitamin A and thyrotropic hormone has been established by animal experimentation.[58] In our patient two basal metabolic determinations made in the early days of her present hospital admission were recorded as plus 12 and plus 10. However, during this period the bone pains were so severe that one could question whether she was in a truly basal state. The protein-bound iodine was repeatedly lower than normal during the present hospital admission. The radio-active iodine uptake three weeks after discharge from the hospital was normal. Our case does not substantiate or deny the thyroid relationship found in experimental studies with vitamin A.

Two and a half weeks after withdrawal of vitamin A excess, pruritus had completely disappeared. In one month the texture of the skin had improved. In two and a half months, lanugo hairs reappeared, the eyebrows became heavier and the scalp hair was more profuse. Pigmentation was not altered.

HEMORRHAGIC MANIFESTATIONS

Hemorrhage is a prominent feature of vitamin A intoxication in animals and often leads to death even in the absence of trauma. The hemorrhages were shown by Light et al.[59] to be the result of hypoprothrombinemia and were controlled by the simultaneous administration

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amin K. No consistent hemorrhagic phe-
na have been observed in children al-
h sporadic instances of epistaxis were
. The child reported by Josephs had a
onsillectomy hemorrhage. No abnormal
ng was found in the adult patient reported
ilzberger, while Bifulco's patient had a
hemorrhage following dental extractions.
were empirically treated with vitamin K
he bleeding was controlled. There were no
s to ascertain the mechanism for these
rrhages. In our patient there were no
rrhagic manifestations. Her menstrual
was consistently normal, and she under-
dental extractions, bone biopsy and skin
without excessive bleeding. Studies of
rombin levels, prothrombin consumption,
platelets, bleeding and coagulation time
ll normal.

SUMMARY AND CONCLUSIONS

ase of chronic hypervitaminosis A in a
-eight year old white female is described.
a period of eight and a half years she was
alized ten times because of complaints
ble to vitamin A intoxication. Many
ses had been made, including brain
, serous meningitis, chronic encephalitis,
radiculoencephalitis, psychoneurosis and
alized infectious arthritis. Her bizarre
l picture led to additional investigations
clude Addison's disease, dermatomyositis
patitis. In an effort to provide symptomatic
many measures had been undertaken.
included a subtemporal decompression
relief of increased intracranial pressure,
plication of body spicas, fever therapy,
herapy and physiotherapy. During this
period our patient was allowed to con-
the daily consumption of 500,000 units of
n A because of the supposed beneficial
on "ichthyosis" of the skin.

en the clinical diagnosis of hypervitamino-
was finally proposed, a fasting vitamin A
level of 2,000 μg. per 100 cc., the highest
ecorded, was disclosed.

y estimations of the total vitamin A, in-
g the free alcohol and ester fractions, were
over a period of two and a half months.
fluence of menstruation, surgery, cortisone,
ion and alcohol consumption was noted.
ated by previous reports concerning the
nship of vitamin A to nephrolithiasis,

determinations of the blood levels and urinary excretion of calcium, phosphorus and citric acid were made. Blood analysis for phospholipid phosphorus, total fatty acids, and total lipids were carried out because of their role in vitamin A metabolism. Blood carotene levels were studied to emphasize their independence of the vitamin A levels attained by the ingestion of pure vitamin A.

The clinical manifestations of chronic vitamin A toxicity are reflected in the neurologic, skeletal and dermatologic systems. Persistent, severe headache with visual disturbances in the absence of focalizing neurologic signs may occur in hypervitaminosis A. This is the result of increased intracranial pressure due to excessive production or decreased absorption of cerebrospinal fluid. In our patient a subtemporal decompression had been performed elsewhere after a diagnosis of serous meningitis had been made.

Bone pains are usually present in chronic vitamin A intoxication. X-ray evidence of bone involvement has not been previously described in adults. In our case x-ray and bone biopsy studies indicate that the fundamental disturbance consists of calcification with or without true bone formation in the pericapsular, ligamentous, tendinous and subperiosteal tissues. The pain and the progressive crippling deformities in our patient had been previously considered the results of generalized infectious arthritis. The differences between Marie-Strümpell arthritis and vitamin A toxicity are discussed in detail.

The dermatologic manifestations of vitamin A toxicity include pruritus, fissuring and soreness at the corners of the mouth, coarsening of the hair with alopecia, loss of the fine lanugo hairs of the extremities and pigmentation.

Hemorrhagic manifestations during vitamin A toxicity have been considered by others to be of clinical significance. Our patient failed to show any hemorrhagic tendencies. Laboratory studies likewise showed no disturbance in any of the factors related to the clotting mechanism. Because of interest in the relationship of vitamin A to thyroid activity tests were made of the basal metabolism, protein-bound iodine and radioactive iodine uptake. These showed no consistent pattern of altered thyroid activity.

Clinical improvement in the neurologic, skeletal and skin manifestations took place rapidly upon stopping excess vitamin A intake.

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This rapid response is a most important point in the differential diagnosis.

Treatment with massive doses of vitamin A now recommended in many clinical conditions must be reviewed from the standpoint of potential toxicity. If these large doses are to be used, rest periods should be instituted and determinations of the vitamin A blood level made. Self-medication with vitamin concentrates containing large doses of vitamin A is a common occurrence due to the general belief by the laity that vitamins improve health and increase resistance to infection.

Acknowledgment: The authors wish to thank Dr. Bernard S. Epstein, for assistance with the radiographic studies; Mr. Bruno Elkan, for technical assistance; and Miss Audrey Daniels, for clerical assistance. We are indebted to Drs. Charles Solomon and Alexander Davidson for their cooperation.

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Chronic Vitamin A Poisc

A Case Report

ROBERT B. TUDOR, M.D.
Bismarck, North Dakota

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THYROTOXIC CASES [illegible] of poisoning due to chronic overdosage with vitamin A have been reported. Josephs[1] reported the first case in 1944. severe hypervitaminosis A occurring in a boy 3 years of age who had received about 240,000 U.S.P. units of vitamin A daily for thirty-three months. The effects of excess vitamin A on animals were first described by von Drigalski,[22] Collazo and Sanchez-Rodriguez,[23] Moore and Wang,[24] and Domagk and von Dubenreck.[25]

CLINICAL FINDINGS

The chief symptoms are a long latent period, irritability, anorexia, scaly skin eruption, pain along the bones most exposed to trauma, swollen legs and forearms, pruritus, alopecia, cracked and bleeding lips, and tender swellings of the skull. Hepatosplenomegaly, hyperpigmentation, persistent severe headache, exophthalmos, papilledema, and a craving for butter may be present. A massive dose of vitamin A may cause an acute, benign hydrocephalus.[26]

RADIOLOGIC FINDINGS

Roentgenograms have shown hyperostoses of the bones involved, osteolytic mottling of epiphyses, thinning of the calvaria, decalcification of the skull and vertebrae, and calcification of periangular structures.

ROBERT B. TUDOR, a 1935 graduate of the University of Minnesota, is on the staff of the Bismarck and St. Alexius Hospitals and the department of pediatrics, Quain and Ramstad Clinic, Bismarck, North Dakota.

Biopsy [illegible] thicke[ned] calcifi[cation] shown eratic tilage, tende[rness] min A in hu[mans].

S. M., [illegible] 13, 19[illegible] 3 lb. 1 [illegible] swallow had be[en] last fe[d] another 1952, [illegible] veaked weight [illegible]. He was a very [illegible] nal. The glands were not enlarged. Bilateral tender occipital masses and massive frontal craniotabes were present. The hair was sparse. The throat was inflamed. The ears were normal. The heart was normal. The lungs were clear. The liver, spleen, and kidneys were not palpable. The extremities were not tender. The reflexes were normal. Accessory clinical findings showed hemoglobin 74 per cent, white cell count 15,200, polys 13, lymphs 70, and eosinophils 3 per cent. Throat culture showed alpha streptococcus. Blood culture was sterile. Routine agglutinations were normal. Peripheral blood smear was normal. Urinalysis was normal. Blood calcium was 11.5 and phosphorus 5.0. Alkaline phosphatase was 3 King-Armstrong units. Lumbar puncture showed 2 mononuclear cells, normal sugar, and 10

On August 14, 1952, it was discovered that the child had been taking 1 tsp. a day of Navitol with Vitamol, approximately 250,000 units of vitamin A, since January 1952. Blood vitamin A level was 602 gamma and carotene level was 472 gamma. (Normal level for vitamin A is 20 to 60. Normal level for carotene is 20 to 200.) The child did not crave butter. The Navitol was discontinued and he was discharged from the hospital August 15, 1952.

DISCUSSION

The toxic factor in vitamin A poisoning is said to be the permanently elevated plasma vitamin A level. Clinical hypervitaminosis A develops only after the liver is loaded with the vitamin so that it is no longer able to remove from the circulation the excess amount ingested. Hepatic dysfunction may be the basis for the vitamin A poisoning. Faulty or limited excretion may contribute to maintenance of high blood levels.

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Current Clinical Reviews

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Chronic Vitamin A Poisoning;

A Case Report

ROBERT B. TUDOR, M.D.
Bismarck, North Dakota

THIRTY CASES [1-21] of poisoning due to chronic overdosage with vitamin A have been reported. Josephs[1] reported the first case in 1944. severe hypervitaminosis A occurring in a boy 3 years of age who had received about 240,000 U.S.P. units of vitamin A daily for thirty-three months. The effects of excess vitamin A on animals were first described by von Drigalski.[22] Collazo and Sanchez-Rodriguez,[21] Moore and Wang,[20] and Dunagk and von Dobrowsck.[23]

CLINICAL FINDINGS

The chief symptoms are a long latent period, irritability, anorexia, scaly skin eruption, pain along the bones most exposed to trauma, swollen legs and forearms, pruritus, alopecia, cracked and bleeding lips, and tender swellings of the skull. Hepatosplenomegaly, hyperpigmentation, persistent severe headache, exophthalmos, papilledema, and a craving for butter may be present. A massive dose of vitamin A may cause an acute, benign hydrocephalus.[20]

RADIOLOGIC FINDINGS

Roentgenograms have shown hyperostoses of the bones involved, occasional mottling of epiphyses, thinning of the calvaria, decalcification of the skull and vertebrae, and calcification of pericapsular structures.

PATHOLOGY

Biopsy has been done in 2 cases, and has shown thickening of the periosteum with secondary calcification. In rats[27] excess vitamin A has been shown to cause acceleration of periosteal proliferation, rapid consumption of epiphyseal cartilage, and remodeling of bone attended by osteoclasis. Hemorrhages[20] are common in vitamin A poisoning in animals, but are uncommon in humans. They are due to hypoprothrombinemia.

CASE HISTORY

S. M., a 20-month-old white male, was first seen August 13, 1952, because of irritability. His birth weight was 5 lb. 9 oz. He had diphtheria, pertussis, tetanus, and smallpox immunizations before the age of 1 year. He had had no previous illness. On August 5, 1952, he had fever and diarrhea. About August 8, 1952, the mother noted swellings of the occiput. On August 9, 1952, he was given a penicillin shot. Examination revealed that the temperature was 103.8° rectally. The weight was 27½ lb.; the head circumference was 36½ cm. He was a very irritable child. The skin was normal. The glands were not enlarged. Bilateral tender occipital masses and massive temporal craniotabes were present. The hair was sparse. The throat was inflamed. The ears were normal. The heart was normal. The lungs were clear. The liver, spleen, and kidneys were not palpable. The extremities were not tender. The reflexes were normal. Accessory clinical findings showed hemoglobin 74 per cent, white cell count 13,300, polys 13, lymphs 70, and eosinophils 3 per cent. Throat culture showed alpha streptococcus. Blood culture was sterile. Routine agglutinations were normal. Peripheral blood smear was normal. Urinalysis was normal. Blood calcium was 11.3 and phosphorus 5.0. Alkaline phosphatase was 3 King-Armstrong units. Lumbar puncture showed 2 mononuclear cells, normal sugar, and 10 mg. of protein. Roentgenograms disclosed a normal chest, periostitis of the long bones, and thinning of the cranial bones. Bone marrow aspiration was found to be normal.

On August 14, 1952, it was discovered that the child had been taking 1 cap. a day of Natrol with Vitamins, approximately 200,000 units of vitamin A, since January 1952. Blood vitamin A level was 694 gamma and carotene level was 472 gamma. (Normal level for vitamin A is 20 to 40. Normal level for carotene is 20 to 260.) The child did not crave butter. The Natrol was discontinued and he was discharged from the hospital August 15, 1952.

He was next admitted to the hospital August 19, 1952, because of a head injury. At this time, because of a hemoglobin of 41 per cent, he was given a blood transfusion. Roentgenograms disclosed a fracture of the right parietal bone.

He was next seen September 2, 1952. The head circumference was 30 cm. The hemoglobin was 68 per cent. The weight was 26½ lb. There were no tender swellings of the head. Temporal craniotabes were still present.

On January 13, 1953, the temperature was 99.4° rectally. The weight was 28 lb. The head circumference was 31 cm. The hemoglobin was 72 per cent. There was no craniotabes. The vitamin A level was 37.8 gamma per cent. The carotene level was 468 gamma per cent.

On June 29, 1953, the weight was 32 lb. There were no complaints and no unusual physical findings. The vitamin A level was 38.5 gamma per cent and the carotene level was 386 gamma per cent.

DISCUSSION

The toxic factor in vitamin A poisoning is said to be the permanently elevated plasma vitamin A level. Clinical hypervitaminosis A develops only after the liver is loaded with the vitamin so that it is no longer able to remove from the circulation the excess amount ingested. Hepatic dysfunction may be the basis for the vitamin A poisoning. Faulty or limited excretion may contribute to maintenance of high blood levels.

SUMMARY

The case of a 20-month-old child who developed signs of vitamin A poisoning after ingesting 200,000 units of vitamin A daily for eight months has been discussed. Craniotabes which occurred in this patient has been reported in the literature in only 1 other patient with vitamin A poisoning.[11]

ADDITION

Since the preparation of this paper, Geman has reported the case of an adult who developed asterognosis and onycholysis after taking 50,000 to 100,000 units of vitamin A daily for eight months, in Queries and Minor Notes, J.A.M.A. 155:947, 1954.

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Saunders and Wallace Co. 421 pages. $10.00.

For anyone interested in genetics and inheritance and also in environmental effects, this book will be invaluable. As always in this series of researches, the articles were written by nationally known experts. Included in the volume are subjects such as Principles of Human Constitution, Genetics and Physiology of the Nervous System, Genetic Factors which Affect the Susceptibility and Resistance of the Nervous System to Virus Diseases, and Inherited and Acquired Components of Behavior. There is even an article on the Practical Affairs of Nutrition. Also included are articles on behavior patterns and early human fetal behavior.

Today many investigators will be much interested in the chapter by Bertalanffy on the Genetics of Lipidoses. Many abnormalities of brain function appear to be due to hereditary disturbances in the chemistry of the brain. These defects are particularly well covered in the article Hereditary Lipidoses. As many persons know today, infants who lack the ability to handle phenylketonuria acid are always mentally underdeveloped.

There is a good article on The Inheritance of Neuromuscular Diseases and one on Hereditary Ataxias. Seizures, brain waves and inheritance in epileptic twins are also discussed.

Also included are discussions of the genetics of psychotic behavior patterns and the genetic aspects of adaptability.

This book ought to be read by all thoughtful physicians. It certainly ought to be read by all psychiatrists.

WALTON C. ALVAREZ, M.D.

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Aging—General Aspects. Ciba Foundation Colloquia on Aging—Vol. I. edited by G. E. W. Wolstenholme and Maeve O'Connor. Boston: Little, Brown & Co. 225 pages. $6.75.

This volume is a presentation of the papers and discussions of 34 participants at a Ciba Foundation Symposium in July 1954 on Aging, dealing with its general aspects. Many of the leading scientists in gerontology participated and the contributions constitute a major contribution to the current literature in the field. Much attention was paid to chemical and biochemical studies of tissues and organs in relation to age. A healthy emphasis was placed upon the importance of the study of changes in frequency of various types of disease resulting from changed environment in ageing. Studies in experimental animals, the authors still the of specific disease processes in old age and longevity studies must include observations on diets as major causes of death to be significant.

Another important point brought out is that the current assumption in child-bearing that late growth rates are desirable, may be quite fallacious. To the contrary, it may be entirely possible that early undernourishment, especially in calories, would be much more conducive to a healthy long life.

This volume is well illustrated, characterized, and indexed and should be of interest to every student of the ageing problem.

MAURICE B. VISSCHER, M.D.

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Normal Labor. by LEROY A. CALLAN, M.D., 1955. Springfield, Illinois: Charles C Thomas. 126 pages. Illustrated. $4.50.

The first half of this monograph represents original writing for this publication; the latter half consists of reprints of previously published material.

The former is a review of the author's twenty-five years of experience and deals with labor, in being the author's thoughts on etiology of the onset of labor and studies of the first, second, and third stages of normal labor.

The author feels that the etiology of onset of labor is divided into a neurogenic phase and extra-progestin isolation phase. The accumulation of oxytocin to the point of initiating contractions may be of importance.

In determining the end of the first stage, the author stresses not only

contractions, and dilation of a single centimeter are important in determining the effectiveness of labor. Determination and classification of the abnormalities are discussed. A rather cumbersome and lengthy method of predicting length of labor is detailed.

A modification of Williams' technic for management of the third stage of labor contains much valuable information.

The author, surprisingly, leaves the problem of breast feeding and circumcision of the male infant to the pediatrician.

The latter half of the monograph is made up of 7 previously published papers which enlarge on certain phases of labor.

JAMES R. REAGHEY, M.D.

•

Hysterectomy, by JOHN C. BURCH and HERMAN T. LAWRY, 1954. Springfield, Illinois: Charles C Thomas. $5.50.

This small volume of 85 pages is another of the monographs of the American Lecture Series. The authors are professor and instructor, respectively, of gynecology at Vanderbilt University School of Medicine. A discussion of the general philosophy of hysterectomy is presented, its indications, and the technic as used by the authors. Complications of surgery are also discussed.

Some literalistic evidence as to the future risk of destruction by uterine cancer is given and discussion in its relation to clinical decisions in the handling of such conditions as "functional uterine bleeding." In general, the authors' conclusions concerning indications are those which are generally accepted. The surgical technics vary little from those usually applied except that in both abdominal and vaginal hysterectomy, the vagina is not closed.

A good deal of opinion and argument are expressed, but unfortunately little to the way of proof is presented. In general, however, it is a clear and logical exposition of the problems concerned.

The volume is attractively printed on glossy paper which takes the illustrations well. An extraordinary number of excellent illustrations of surgical technics are included which were produced by Helen Lorraine. These illustrations will be useful both for teaching and for the beginner.

J. L. MCKELVEY, M.D.

Transactions of the North Dakota State Medical Association

Sixty-Eighth Annual Meeting

Bismarck, North Dakota, April 30, May 1, 2, and 3, 1955

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HYPERVITAMINOSIS A

E251

BY

J. D. PICKUP

From Wakefield General Hospital

(RECEIVED FOR PUBLICATION FEBRUARY 28, 1956)

Since Josephs (1944) first described hypervitaminosis A there have been numerous cases reported in the American literature, notably by Toomey and Morisette (1947) and by Caffey (1950 and 1951). No record of such cases has been traced in the British literature and so the occurrence of two examples of this condition is thought to be worthy of record.

Case Reports

Case 1. R.P., a boy of 6 years, was admitted to the Wakefield General Hospital on March 9, 1955. He had had frequency of micturition and nocturnal enuresis for two weeks. This was followed by vomiting and anorexia for one week. Then he developed pain in the arms, legs and forehead of such severity as to prevent him from sleeping. He was thought to have lost weight during the previous three weeks.

Xeroderma had been diagnosed at the age of 5 months and had been treated by ointment until a dermatologist prescribed 'avolcum', a dram b.d. This was continued until six weeks before admission when the dose was increased, probably by the mother, to 'avolcum', drams 2 b.d. It was estimated that the intake of vitamin-A over the six weeks before admission was about 463,040 i.u. per day.

On admission the child was ill and fretful with a temperature of 100° F. The skin was salmon pink and scaling. The lips and nasal mucocutaneous junctions were cracked and bleeding, and very sore. The arms and legs were extremely tender to the lightest touch, subcutaneous tissues were swollen, most markedly over the tibiae. The liver and spleen were both enlarged three fingerbreadths below the costal margin. There was a bilateral conjunctivitis.

During the first week in hospital the skin became more scaly and the patient continued to complain of pain in the upper limbs and back which caused difficulty in sitting. Oedema of the face developed on March 13. The temperature dropped to normal by the end of the week.

A radiograph of the chest was normal (March 9).

On March 10 the haemoglobin was 93%, and the total white blood cell count 10,600 per c.mm. (neutrophils 60%, lymphocytes 38%, monocytes 2%). The E.S.R. was 17 mm. in one hour. The Mantoux test (1 : 1,000) was negative.

On March 11 the blood cholesterol level was 316 mg. per 100 ml.

On March 12 albumin + was found in the urine, and also occasional hyaline and granular casts and very occasional pus cells.

On March 15 the cerebrospinal fluid was normal. The blood urea level was 88 mg. per 100 ml.

During the second week the pain in the limbs and back subsided, and by the end of the week a considerable improvement in the skin was noticed, it being quite soft and moist. The dry, cracked lips persisted. On March 18 the prepuce swelled. The spleen was slightly smaller.

A radiograph of the skull and limb bones on March 17 showed normal appearances.

The serum bilirubin level was 0·3 mg. per 100 ml.

A trace of albumin and a few pus cells were found in the urine.

On March 21 a water dilution and concentration test was normal.

Thymol turbidity was 3 units.

The alkaline phosphatase level was 25·2 units per 100 ml.

The blood carotene was 20 µg. per 100 ml. and the blood vitamin A, 450 i.u. per 100 ml. (normal 50-130 i.u. per 100 ml.).

The oedema of the prepuce had cleared by the third week, and, apart from cracked lips (Fig. 1), the boy was

FIG. 1.—Hypervitaminosis A showing cracked and bleeding lips.

free of symptoms. The liver had reduced slightly in size, and the urine was normal. On March 26 the blood urea level was 40 mg. per 100 ml.

At the end of the fifth week the hair was being shed

and the scalp became scaly. The rest of the skin was in good condition.

FIG. 2.—Hypervitaminosis A showing loss of hair.

On April 4 the blood urea level was 21 mg. per 100 ml., and the urine normal.

On April 6 alkaline phosphatase was 32 units per 100 ml., serum calcium 10·5 mg. per 100 ml. and blood cholesterol 187 mg. per 100 ml.

By the end of April the boy's hair was shed in handfuls (Fig. 2). The skin was becoming dry and ichthyotic. The spleen and liver, although reduced in size, were still palpable.

A radiograph of the clavicle on April 25 was normal. The left humerus showed an area of osteoporosis in the upper third of the shaft.

On April 26 the blood carotene level was 20 µg. per 100 ml., and the blood vitamin A 150 i.u. per 100 ml.

On April 27 the blood urea level was 22 mg. per 100 ml., haemoglobin 86%, E.S.R. 12 mm. in one hour. The total and differential white blood counts were normal.

On April 28 the alkaline phosphatase level was 37 units per 100 ml.

On May 23 the blood carotene level was 30 mg. per 100 ml., and the blood vitamin A 90 i.u. per 100 ml.

On May 27 the thymol turbidity was 1 unit per 100 ml. and alkaline phosphatase 26·9 units per 100 ml.

On August 9 the child was well but the liver and spleen were still just palpable. The skin was ichthyotic but the hair was growing well.

Case 2. S.W., a girl aged 4 years, was admitted to the Clayton Hospital, Wakefield, on April 12, 1955. The complaint was of anorexia and malaise, pains in the forehead, wrists, forearms and shins, and facial and temporal swelling for two weeks. There was a loss of weight during the same period. There had been severe epistaxis and also pain and discharge from the ear during the previous two days.

The child had no previous illness apart from ichthyosis for which she had been given 'avoleum', 1 dram t.d.s. (347,230 i.u. per day), from a dermatological department for the past two years.

On admission the child had a temperature of 101° F. She had a scaling, patchy erythematous rash on the upper parts of the arms and trunk. The lips were crusted and bleeding. There was oedema of the eyelids, and the temporal regions were so swollen that the face had a triangular appearance. The shins and forearms were tender to the lightest touch.

The liver was enlarged two fingerbreadths below the costal margin. The spleen was impalpable.

There was a bilateral otitis externa with an underlying otitis media on the right side. The throat was injected.

During the first week in hospital the general condition slowly improved and the temperature was normal in five days. The facial and temporal swelling subsided in three days, but the eruption became more extensive, covering the forearms and abdomen with erythematous patches (Figs. 3 and 4). The skin became dry and scaling and the lips cracked. The tenderness over the long bones became gradually less and at the end of the week there was only slight tenderness over the tibia.

Treatment with penicillin cleared the ear infection. The size of the liver became slightly less.

FIG. 3.—Hypervitaminosis A showing macular rash in the early stage.

On April 13 haemoglobin was 78% (11·6 g.), W.B.C.s 12,800 c.mm. (polymorphs 85%, lymphocytes 13%, monocytes 2%). The E.S.R. was 17 mm. micro in one hour.

The urine showed albumin + and reduced Benedict's

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solution. A chromatogram showed glucose. There were a few pus cells and casts.

A swab from the ears on April 14 yielded a heavy growth of penicillin-sensitive *Staphylococcus aureus*.

FIG. 4.—Hypervitaminosis A showing macular rash in the acute stage.

Radiographs showed that both mastoid regions appeared normal and a little generalized congestion in the chest.

Radiographs of the wrist and arms on April 15 showed increased density at the growing ends of the shafts of the long bones but no actual irregularity, and no abnormality of the spine and clavicles.

On April 19 the blood carotene level was 20 µg. per 100 c.c. and blood vitamin A 700 i.u. per 100 ml.

By the end of two weeks the child was in good general health. The rash and facial swelling had gone but the skin was dry. At the beginning of the third week the hair became dry and lifeless and could easily be pulled out, and soon was shed in handfuls, only a sparse growth remaining. The liver was only just palpable.

On April 26 the blood urea level was 34 mg. per 100 ml. A three-day vitamin C saturation test when 125 mg. ascorbic acid was given each day, gave daily excretions of 2·1, 2·1 and 3·9 mg. (normal for weight 12·5 mg.).

On April 28 the alkaline phosphatase was 41 units per 100 ml., serum phosphorus 2·9 mg. per 100 ml., serum calcium 10·3 mg. per 100 ml. and serum cholesterol 140 mg. per 100 ml.

By July 12, 1955, the hair was growing. The liver and spleen were not palpable. The skin was normal.

On review on November 11 the ichthyosis was returning; the hair was normal and the child well.

Discussion

It has long been known that polar bear's liver produces acute vitamin A poisoning. Rodahl and Moore (1943) found that the vitamin A content of the liver was equivalent to 8,000,000 i.u. in 0·5 kg. The symptoms produced are headache, hyperirritability followed by drowsiness, desquamation of the skin at the mucocutaneous junctions in 24 hours, with peeling of the entire skin in a few days.

Chronic poisoning due to vitamin A has been well described by Caffey (1950 and 1951) following on the earlier descriptions by Toomey and Morissette (1917) and Josephs (1944).

In nearly all the cases described previously the poisoning was due to excessive and prolonged administration of either halibut liver oil or oleum percomorphum. I have not been able to trace any previous record of a case due to a pure vitamin A product such as 'avoleum'.

From the previous accounts a fairly uniform clinical picture can be drawn. The initial symptoms are usually anorexia, fretfulness and itching of the skin. Tender subcutaneous swellings appear over the long bones and skull. Fissures appear on the lips and other mucocutaneous junctions with cracking and bleeding of the mucosa. Cortical thickening of the long bones is usual after the vitamin has been given for six to 15 months. In neither of the above cases was this found, although in Case 2 it was thought that early changes in the long bones could be seen, but the appearances were not very convincing.

The absence of changes in the bones in Case 1 might be due to the fact that a very high dosage was given for only six weeks before symptoms appeared.

Caffey (1950) notes that there is a latent period of several months between the start of the excessive dosage and the appearance of diagnostic clinical signs. The length of this period did not depend on the size of the overdose and the shortest latent period was six months. In his series the earliest radiological observation, showing cortical hyperostosis in the ulnas, was three weeks after the onset of symptoms. It may be that in the two cases described here that as this interval was less than that period the hyperostosis had not time to develop.

Loss of hair and dryness of the skin associated with an erythematous rash also characterize the condition. Both our patients had this typical scaly erythematous rash on the trunk in the early stages of the illness and both lost much of their hair (Fig. 2). After the vitamin A was stopped and the rash had cleared there was a period in which the skin was soft in texture and normal in every way, but this was ultimately followed by a relapse to the ichthyotic

state. This period in which the skin was normal was presumably sustained by the gradual release of vitamin A stored in the liver.

The liver and spleen are often found to be enlarged in hypervitaminosis A and in Case 1 both are still palpable 10 months after admission. This leads one to think that serious and permanent liver damage may be produced by prolonged administration of the vitamin, and makes one wonder whether the possible toxic effects should be lightheartedly dismissed as in some recent statements.

The most characteristic feature of the condition is that once the vitamin A is stopped the signs and symptoms regress and there is rapid recovery. The tenderness, pain, anorexia and irritability usually disappear within one week.

The most valuable investigation is the estimation of the vitamin A blood level showing a rise above the normal level of 50-130 i.u. per 100 ml.

The one condition with which vitamin A poisoning may be confused is infantile cortical hyperostosis. Caffey (1950) pointed out that the latter condition always appears in the first four months of life, whilst hypervitaminosis A is usually not seen before the end of the first year. He states that cortical thickening of the bones is seen in both conditions, the face and jaw are swollen and the mandible thickened in every case of infantile cortical hyperostosis, these structures being unaffected in vitamin A poisoning. The blood levels of vitamin A are normal in cases of infantile cortical hyperostosis.

In conclusion it should be emphasized that the dosage of 'avoleum' recommended by the manufacturers is unlikely to produce symptoms. It would appear that in the treatment of skin conditions by vitamin A care should be taken if it is required to use high dosage for very long periods.

I wish to thank the Editor of the *Proceedings of the Royal Society of Medicine* for permission to publish these cases which were previously reported at the Section of Paediatrics meeting on June 25, 1955 (*Proc. roy. Soc. Med.*, 48, 1107).

I am grateful to Dr. W. L. Rose for the numerous biochemical and pathological investigations, and to Dr. G. A. Stevenson and Dr. A. M. Fraser for radiological reports. Dr. A. T. Haworth, of the Department of Chemical Pathology of the University of Leeds, kindly estimated carotene and vitamin A blood levels. Dr. J. M. Moffitt gave much valuable assistance in the preparation of the manuscript, and Mr. Wade, the Librarian of the Royal Society of Medicine, helped greatly in compiling the references. British Drug Houses Ltd. gave much valuable advice on the strength of 'avoleum' and the toxic effects of vitamin A.

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JAMA 161:1157-59 (July 21) 1956

HYPERVITAMINOSIS A

REPORT OF A CASE IN AN ADULT

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and
Robert L. Dryer, Ph.D., Indianapolis

Although there has been a steady increase in the number of reports of clinical hypervitaminosis A occurring in children since the condition was first described in a child by Josephs,[1] in 1944, only four cases[2] of chronic hypervitaminosis A have been reported in adults. The present report describes chronic hypervitaminosis A occurring in a young adult woman.

A 21-year-old woman was first seen on July 24, 1954, because of pain in both legs and ankles that had persisted for one week. Increasing fatigue and insomnia had been present for approximately two months. She had had intermittent low back ache and mild bilateral hip pain for one month. There were complaints of occasional aching pain in the left elbow and intermittent severe aching pain in the left foot, which at times made walking difficult. Slight swelling of both ankles and a bluish discoloration on the outer aspect of the right ankle, without a history of trauma, were known for one week. Twice in the preceding two months she had a sore mouth, with small blisters on the sides of the tongue. Frequency of urination had been present for one week. Her appetite had remained good, there was no weight loss, and the menstrual cycle was not altered. Review of her history revealed that her left ovary was removed when she was 18 months of age; the diagnosis had been "fibrous tumor." When she was 19 years of age an intracanalicular fibroadenoma had been removed from the left breast. She had a hymenotomy in May, 1954, for congenital hymenal stenosis. She gave a six-year history of moderately severe acne of the face and upper thorax, treated at various times with diet, lotions, x-ray, and vitamins. Her family history revealed that she was an only child. Her parents were living and well.

On further questioning it was learned that the patient had

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taking multiple-vitamin capsules for acne from March to July, 1933, by prescription from a dermatologist. The capsules were taken three times a day, and each capsule contained 10,000 units of vitamin A. Vitamins were also administered intramuscularly on several occasions during this period. There was apparent improvement in the condition with this treatment. With exacerbation of the acne in December, 1933, she resumed the use of vitamin A without consulting the dermatologist. She purchased, without prescription, vitamin A capsules that contained 50,000 units per capsule and faithfully took one capsule three times a day. This vitamin intake was supplemented with multiple-vitamin capsules that contained 10,000 units of vitamin A per capsule, and she took from one to three of these each day. This schedule was maintained without interruption from December, 1933, until July 21, 1934. During this period of high vitamin A intake she noted that her hair became less oily but was not difficult to manage. Her nails seemed stronger. Her skin was not oleariferous but recently became more oily, and there was desquamation of skin around the acne eruptions.

On physical examination the patient was an alert, cooperative, intelligent woman, 5 ft. 3 in. (160 cm.) tall and weighing 100 lb. (45.4 kg.). She did not appear ill. The blood pressure was 110/70 mm. Hg, pulse 76 per minute, and respirations 20 per minute. Acneform eruptions were noted on the face and upper thorax. There was desquamation about some of the lesions. The skin was otherwise normal. The distribution and texture of her hair were normal. The fingernails were normal. The examination of ears, eyes, nose, mouth, and pharynx was not remarkable. The thyroid gland was not palpable. No masses were felt in the breasts. The lungs were clear to auscultation and percussion, and the heart was normal. Her abdomen was soft and flat. The liver edge was palpated 3.5 cm. below the right costal margin in the midclavicular line on deep inspiration and was not tender. No other organs or masses were felt. Skeletal examination revealed a mild dorsolumbar scoliosis centered at T-10. There was moderate tenderness on percussion over both tibias. There was no tenderness on percussion over the other long bones or the vertebral spines. A yellow-green discoloration of the skin, approximately 4 cm. in diameter, was noted anterior to the lateral malleolus of the right ankle. There was no pretibial or ankle edema. The rectal examination was normal. X-ray examination of the long bones revealed no abnormalities. There was no roentgenologic evidence of periostitis.

Laboratory studies on July 26, 1934, were as follows: hemoglobin value 14.6 gm. per 100 cc., red blood cell count 4,450,000 per cubic millimeter, white blood cell count 7,350 per cubic millimeter, polymorphonuclear leukocytes 67%, lymphocytes 29%, monocytes 2%, eosinophils 1%, basophils 1%, serum albumin 4.02 gm. per 100 cc., serum globulin 1.88 gm. per 100 cc., serum alkaline phosphatase 2.2 King and Armstrong units, direct serum bilirubin 0.2 mg. per 100 cc., indirect 0.6 mg. per 100 cc., prothrombin time 14.9 seconds (control 15 seconds), thymol turbidity 1 unit, cephalin flocculation 2+ in 48 hours, total serum lipids 802 mg. per 100 cc. (normal range 385-875 mg. per 100 cc.), serum carotene 151 mcg. per 100 cc. (normal range 80-370 mcg. per 100 cc.), and serum vitamin A alcohol 832 mcg. per 100 cc. (normal range 15-60 mcg. per 100 cc.). Studies on Sept. 22, 1934, revealed a serum carotene level of 170 mcg. per 100 cc. and a serum vitamin-A-alcohol level of 50 mcg. per 100 cc. All blood samples were obtained with the patient in the fasting state.

Three days before she consulted us she had exhausted her supply of vitamin A capsules. With discontinuation of the vitamin A capsules and withdrawal of the multivitamins, no further treatment was indicated. One week after the initial examination all leg and ankle pain had subsided and the tibial tenderness had disappeared completely. The liver edge could still be palpated 1.5 cm. below the right costal margin on deep inspiration. Two weeks after the initial examination there were no subjective complaints and the liver edge was no longer palpable. The acneform lesions persisted. One year later she was free of subjective complaints and physical examination was within normal limits.

Comment

The administration of vitamin A in a dose of 50,000 units three times a day has been cited as a useful adjuvant in the treatment of acne vulgaris when the nature of the lesions suggests vitamin A deficiency.[1] In the case presented this approximate dosage schedule was maintained for over seven months, and vitamin A intoxication resulted. The size and duration of the dose that will produce toxic effects in an adult and the incidence and severity of these effects will vary with the person. The physician administering large doses of vitamin A over a long period of time should be acquainted with the possible manifestations of intoxication.

In all four of the previously reported cases of chronic hypervitaminosis A in adults, loss of hair, bone and joint pains, advanced skin changes, and bone tenderness were described. There was no loss of hair in our patient, and toxic skin manifestations were minimal. Bone and joint pains and bone tenderness were present. Three of the four case reports described symptoms of anorexia, weight loss, and weakness, none of which were noted by our patient. Polyuria, soreness of the mouth and lips, pruritus, exophthalmos, severe headaches, and hepatomegaly have each been reported in two cases. In the case described by Gerber and co-workers,[2a] the hepatomegaly disappeared in the latter years of the illness in spite of continued excessive intake of vitamin A. In our case, frequency of urination, soreness of the mouth, blisters on the tongue, and hepatomegaly were present, but there were no complaints of headache or pruritus, and exophthalmos was not present. Insomnia, night sweats, change in the menstrual cycle, polydipsia, splenomegaly, hemorrhagic manifestations, and x-ray evidence of bone involvements have each been described in one case. Of this group our patient complained only of insomnia. There was an unexplained ecchymosis on the right ankle, but no bleeding tendency was demonstrated, and the prothrombin time was normal. The spleen was not palpable, and x-ray studies of the long bones were interpreted as normal.

The fasting vitamin A blood level of 832 mcg. per 100 cc. reported in our patient is one of the highest ever recorded. There was a moderate increase in total serum lipids. A similar elevation was found in the case in an adult reported by Sulzberger,[2c] whereas Gerber's[2a] patient had a normal total lipid level in the latter years of her illness. Josephs[2b] observed an early rise in serum lipids, with a return to normal later in the course of the illness. An elevated alkaline phosphatase level has been recorded in only one adult patient.[2c] Abnormalities in serum protein and prothrombin time have not been recorded in adults. These determinations were normal in our patient.

Summary

A 21-year-old woman with chronic hypervitaminosis A had ingested 180,000 to 180,000 units of vitamin A daily for over seven months in a program of self-medication for acne. She gave a history of bone and joint pain, fatigue and insomnia, swelling of the ankles,

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...lgesia, soreness of the mouth with blisters on the ...ngue, and frequency of urination. Positive physical ...dings included acne, hepatomegaly, tibial tender... and ecchymosis on the right ankle. X-ray studies ... the long bones were normal. Fasting blood studies ...ped confirm the diagnosis. The symptoms and ...gns disappeared promptly after discontinuation of ... vitamin A medication, and the serum vitamin A ...ated level returned to normal.

... W. Michigan St. (7) (Dr. Elliott).

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EMERGENCY SET TO COMBAT APHYLAXIS

... E. Prickman, M.D.

... A. Lofgren, M.D., Rochester, Minn.

...ments count when one is confronted with a severe ...hylactic reaction such as may follow the admin... of drugs, serums, antigens, antibiotics, local ...thetics, dyes, and contrast mediums to which a ...nt may be hypersensitive, or such as may follow ...ite of a wasp, yellow jacket, or bee to whose ... patient is similarly hypersensitive. The sud..., unexpectedness, and severity of the reaction ...st likely to find the physician unprepared to ... with it promptly and adequately. The anaphy... reaction may take different forms, all of which ...ntially serious and include choking, cyanosis, ..., status asthmaticus, syncope, shock, convul..., stupor, and generalized urticaria and angioneu...edema. The patient may die.

Emergency Set

...prevent anaphylactic reactions, one must always ...t to the problem of drug allergy in its many ... and question the patient as to previous drug, ..., anesthetic, or insect reactions, especially when ... dealing with a patient with known allergy or ... One should never challenge any patient with ...nces to which there is even a questionable ... of hypersensitivity. Nevertheless, anaphylac... actions do occur when least expected, and one ...e prepared. For such emergencies, we have ...ed "anaphylactic sets" and have placed them ...gic areas in the Mayo Clinic, the Rochester ..., and the research and physiology depart-

... Section of Medicine (Dr. Prickman) and the Postoperative ... (Dr. Lofgren), Mayo Clinic and Mayo Foundation. The Mayo ... is a part of the Graduate School of the University of Minnesota.

ments, which are most likely to encounter anaphylactic reactions. The advantage of having all necessary emergency drugs and the equipment for their administration ready in one quickly available tray is obvious. Our anaphylactic sets now contain the following items (see figure): two 1-cc. ampuls of 1:1,000 solution of epinephrine (Adrenalin), two 2-cc. syringes, two hypodermic needles, two long needles (1 in. and 4 in. long), two ampuls of aminophylline (3¾ grains [0.24 gm.] each), one 1,000-cc. bottle of 5% solution of dextrose in distilled water, one intravenous set, one 10-cc. ampul of diphenhydramine (Benadryl) hydrochloride (10 mg. per cubic centimeter), one bottle of hydrocortisone (dilution to 2 cc. gives 50 mg. per

Emergency set to combat anaphylaxis. A, assembled; B, disassembled.

cubic centimeter), one ampul of sterile water, one scalpel, one hemostat, one ampul of absorbable surgical suture (catgut) with needle, alcohol, gauze sponges, swab tongue blade, and one 20-cc. syringe. Other items of an emergency nature could be included, but have been omitted since our primary objective is to be ready to treat anaphylactic reactions adequately and promptly. Although not a part of the assembled anaphylactic set, oxygen (tank and mask) is important and is also readily available in the clinic and hospital areas mentioned. Anyone who has attempted to assemble even a portion of the above items during the stress of caring for an anaphylactic reaction, which can be fatal, will appreciate having these tools ready beforehand for emergency use.

Amer. J. Dis. Child. 95:57-67, 1958

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Progress in Pediatrics

Chronic Vitamin A Intoxication

Report of a Case in an Older Child and Review of the Literature

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Poisoning due to prolonged ingestion of high doses of vitimain A (hypervitaminosis A) in children 3 years of age and younger was first described more than a decade ago. Several cases have also been reported in adults. Recently two children beyond 3 years of age with chronic vitamin A intoxication have been reported from England. The following report describes an additional case in an older child.

Report of Case

A 14-year-old white girl* was admitted to The Children's Hospital on Sept. 11, 1956, with the chief complaint of leg pain of five weeks' duration. Two years prior to admission the patient developed superficial, nonpitting acne vulgaris, for which, 10 months prior to admission, 200,000 units of vitamin A daily had been prescribed by a dermatologist. Two months prior to admission she had had her last normal menstrual period, succeeding ones being at the normal interval but scanty and of one day's duration. About the same time, the patient noted scaling and cracking of her lips and fissuring at the corners of her mouth, for which she used a number of salves without success. Five weeks before admission she began complaining of dull constant pain in her legs, particularly about the knees, aggravated by activity. At this time she was seen by her private physician, who directed that vitamin A be discontinued. This advice was not heeded by the patient, unbeknownst to either her family or the physician. In the month prior to admission leg pain worsened. She walked with a noticeable limp, favoring her left leg, and was unable to continue in gym activities. She observed that her scalp hair became dry in texture and fell out in large quantities with brushing. She also developed a maculopapular eruption on her trunk and desquamation of palms and soles. The family observed during this period that she manifested increasing irritability, but there were no specific symptoms of central nervous system involvement. No bleeding or bruising was noted. Appetite remained good, although the patient was on a self-imposed, rather rigid, diet because of the acne.

Family History.—Noncontributory.

Past History.—Essentially unremarkable. Menarche occurred two and one-half years prior to admission, and menstrual periods had been normal up to the present illness.

Physical Examination.—Weight, 54 kg.; height, 169 cm.; blood pressure, 130/70. Skin: The face (Fig. 1) was the site of superficial nonpitting acne vulgaris and milia. The lips were scaled and cracked, and there were fissures at the corners of the mouth. Over the trunk and to a less degree on the extremities was a fine discrete light tan nonpruritic papular eruption. The skin was dry, and the skin of the palms and soles (Fig. 2) was desquamating in sheets. The underlying skin in

Fig. 1.—Note the superficial acne and the fissuring of the lips. The hair is abundant, though loose. Later alopecia became moderately severe.

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From the Department of Pediatrics, Ohio State University, and The Children's Hospital.

* Permission to report this case was granted by the patient's physician, Dr. Sophie Rogers.

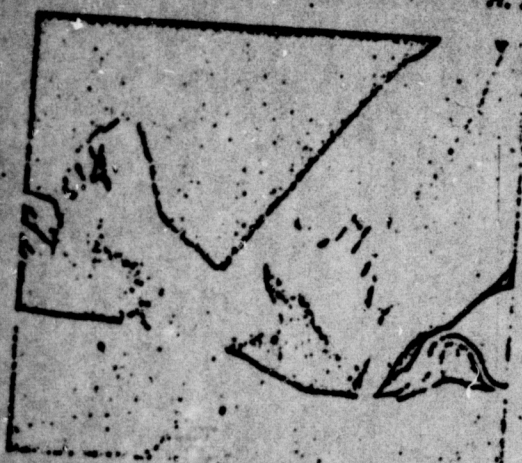

Fig. 2.—This photograph demonstrates the desquamation of the soles of both feet. Similar desquamation was also present on the palms.

these areas was delicate and thin. Nikolsky's sign was absent. The scalp hair was dry and lusterless. There was moderate alopecia. Pubic and axillary hair was normal. Eyes: External examination was normal. There was bilateral papilledema (proved by binocular ophthalmoscopy), and linear hemorrhages surrounded each disc (Fig. 3). Abdomen: Liver and spleen were not enlarged. Extremities: The patient had tenderness in both legs, more on the left, particularly medial and inferior to the tibial tubercle. There was no swelling, heat, or redness. There was no weakness, sensory disturbance, or reflex changes, nor were there signs of meningeal irritation. Mentation was normal to bedside testing.

Laboratory Data.—Hemoglobin, 12.9 gm/100 ml.; white cell count, 8050 per cubic millimeter, with a normal differential count; platelets, normal on appearance. Serum chemistry studies: blood urea nitrogen, 24 mg/100 ml.; CO_2, 21 mEq/liter; chloride, 102 mEq/liter; total base, 149 mEq/liter; total protein, 7.3 gm/100 ml.; albumin, 3.6 gm/100 ml.; globulin, 3.7 gm/100 ml.; calcium, 10 mg/100 ml.; inorganic phosphate, 3.5 mg/100 ml.; alkaline phosphatase, 3.5 Bodansky units; cephalin flocculation, 1+; thymol turbidity, normal; cholesterol, 94 mg/100 ml.; protein-bound iodine, 9.6μg/100 ml. (Sept. 20); repeat, 4.8μg/100 ml. (Oct. 25). B. M. R., normal. Skeletal survey, including long bones, spine, and skull, was normal. Lumbar puncture (supine) yielded crystal-clear fluid, initial pressure 600 mm. H_2O; cells, 3 per cubic millimeter; sugar and protein, normal. EEG, normal. Fasting serum carotine and xanthophyll (Sept. 11), 264μg/100 ml. (normal, 75μg. to 150μg.) and 135μg/100 ml. (normal, 40μg. to 80μg.), respectively. On Feb. 4, 1957, these values were 195μg/100 ml. and 90μg/100 ml., respectively. The fasting vitamin A levels are shown in Figure 4.†

Course.—A diagnosis of chronic hypervitaminosis A was made on admission, and all medications were discontinued. Symptoms and signs began to abate within a week and the patient was entirely asymptomatic, except for continued loose hair, after two weeks. She was discharged on Sept. 17, 1956. When she was examined on Oct. 6, no abnormalities, except alopecia and superficial acne vulgaris (unchanged from before), were noted. Ophthalmoscopic examination was entirely normal, with no residua of the retinal hemorrhages. Regrowth of scalp hair, which was of fine texture, was not observed until six weeks after the vitamin A was stopped. Menstrual periods became normal

†Dr. Gilbert B. Forbes, Department of Pediatrics, University of Rochester School of Medicine and Dentistry, performed the serum vitamin A, carotene, and xanthophyll determinations.

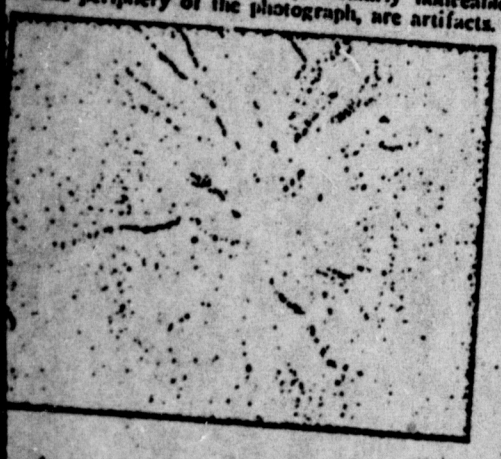

Fig. 3.—Retinal photograph, showing papilledema, venous engorgement, and perivascular hemorrhages, particularly in the right upper quadrant. The oval spots, particularly noticeable in the periphery of the photograph, are artifacts.

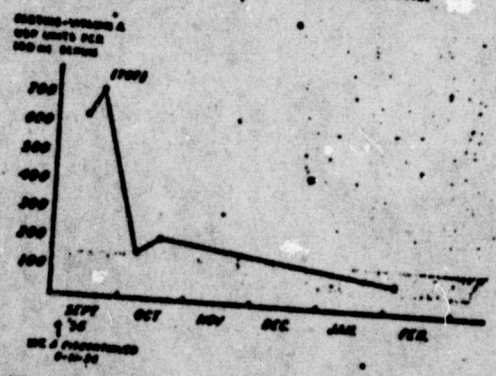

Fig. 4.—Fasting serum vitamin A levels. The shaded area indicates the normal range. Symptoms and signs had subsided by early October (see text), at which time the serum vitamin A level was still elevated.

in duration two months stopped. She has remainer months.

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The first report of c osis A in humans was in 1944, when he desc a 3-year-old child.[1] of 27 reports among has appeared in the I Six cases have been re In 1956, Pickup, in Er first two cases of hyp curring in the British children beyond the a described, namely, 6 a respectively.[2] The presc to be reported in child of age. Thus, a total of vitamin A intoxication They are summarized i

As is illustrated by t symptoms, signs, and can be ascribed chiefly of three systems: the osseous, and the centr The incidence of these and laboratory findings 5. The commonest mar bone pain and tenderne observed in 34 of the 3 and toddlers the pain often been associated swelling without redne tenderness, and swelling

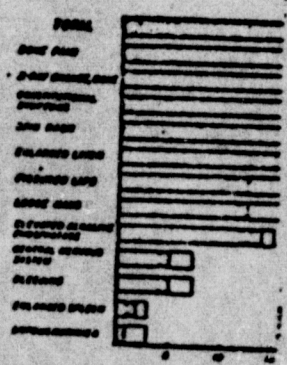

Fig. 5.—Incidence of s laboratory findings of chron in infants-toddlers, older ch

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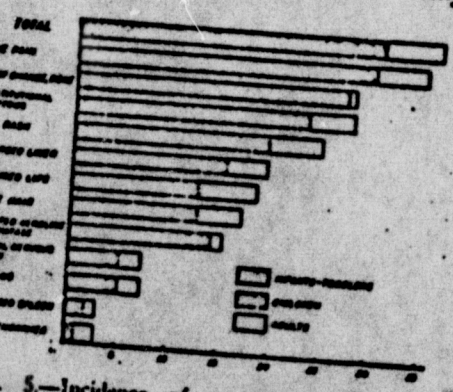
in duration two months after medication was stopped. She has remained asymptomatic for nine months.

Comment

The first report of chronic hypervitaminosis A in humans was recorded by Josephs, in 1944, when he described the findings in a 3-year-old child.[1] Since then, a total of 27 reports among infants and toddlers has appeared in the English literature.[2-18] Six cases have been reported in adults.[19-24] In 1956, Pickup, in England, described the first two cases of hypervitaminosis A occurring in the British Isles.[25] Both were in children beyond the age group heretofore described, namely, 6 and 4 years of age, respectively. The present case is the third to be reported in children beyond 3 years of age. Thus, a total of 36 cases of chronic vitamin A intoxication have been recorded. They are summarized in the Table.

As is illustrated by the present case, the symptoms, signs, and laboratory findings can be ascribed chiefly to the involvement of three systems: the integumentary, the osseous, and the central nervous system. The incidence of these symptoms and signs and laboratory findings is shown in Figure 5. The commonest manifestation has been bone pain and tenderness, which has been observed in 34 of the 36 cases. In infants and toddlers the pain and tenderness has often been associated with subcutaneous swelling without redness or heat. Pain, tenderness, and swelling are most commonly observed over the long bones of the upper and lower extremities. Swelling of the feet due to involvement of the metatarsals is also frequently reported, with pain and tenderness sufficient to limit walking. The occiput has been the site of swelling in several instances. Accompanying x-ray changes have been observed in all infants and toddlers but in only one of the nine children and adults. In the latter instance this consisted of calcification of the infrapatellar ligament and the ligamenta flava. A bone biopsy in that case revealed calcification in the intercartilaginous tissues, with thickened periosteum.[22] The usual x-ray changes consist of cortical hyperostosis similar in all respects to the hyperostosis described in infants by Caffey. Less commonly, mottling or osteoporosis of the bone may be seen. Osteoporosis has not been conspicuous, although in the laboratory animal it is a prominent manifestation, leading to spontaneous fractures. Of interest, however, is the fact that two instances of craniotabes associated with hypervitaminosis A have been observed in the infant group.[12, 18] X-ray changes are most commonly seen in the ulnas, metatarsals, clavicles, and ribs. In none of the reported cases has the mandible been involved. This serves as an important differentiation from infantile cortical hyperostosis.



5.—Incidence of symptoms, signs, and tory findings of chronic hypervitaminosis A nts-toddlers, older children, and adults.

Constitutional symptoms, including anorexia, irritability, failure to gain weight, or actual loss of weight, have been the next commonest symptoms in this group of patients. These symptoms are believed to be related to the bone pain and tenderness and also to pruritis. Anemia has occurred in only a few cases and has been apparently of nutritional type, related most probably to poor appetite.

Involvement of the integument in this disorder consists of three disturbances: skin eruption, fissuring of the lips, and loose hair. The eruption, which frequently is intensely pruritic, most commonly consists of a maculopapular, occasionally slightly pigmented, eruption over the entire

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Summary of Reported Cases of

Chronic Vitamin A Intoxicatio

Case No.	Sex	Vitamin A Dose, Units	Dose Duration, Mo.	Age at Onset of Therapy, Mo.	Age at Onset of Symptoms, Mo.	Age at Diagnosis, Mo.	Bone Pain	Constit. Symptoms	CNS Symptoms or Signs	Menstrual Disorder	Skin Lesions	Loose Hair	Pleural Effusion
Infants													
1	M	240,000+	23	3	26	26	+	+	0	--	0	+	0
2	M	240,000 (6-21 mo.) 240,000 (21-23 mo.)	23	Birth	21	23	+	+	0	--	+	+	+
3	F	240,000 (12 mo.) 480,000 (18 mo.)	30	6	18	36	+	0	0	--	+	+	0
4	M	120,000	13	1	5	14	+	+	0	--	+	+	+
5	F	60,000 (10-16 mo.) 180,000+ (14-27 mo.)	12	10	16	22	+	+	0	--	+	+	+
6	F	180,000	Several	--	10	28	+	+	0	--	0	0	+
7	F	300,000	9	12	19	21	+	+	0	--	0	0	+
8	M	480,000	6	6	11½	19	+	0	0	--	+	0	0
9	M	12,500 (9-17 mo.) 250,000 (17-32 mo.)	15	17	21	32	+	+	0	--	0	0	0
10	M	125,000	6	13	16	18½	+	+	0	--	0	0	0
11	M	180,000	7+	>17	22	24	+	+	0	--	+	0	0
12	M	240,000	17	20	23	27	+	+	0	--	0	0	0
13	F	37,500	17	19	25	29	+	+	+	--	+	+	—
14	M	120,000 (2 wk.-4 mo.) 480,000 (4-16 mo.)	15½	½	5	16	+	+	0	--	+	0	0
15	M	120,000	Many	?	23	24	+	+	0	--	+	0	0
16	F	360,000	24	12	23½	36	+	+	0	--	+	0	+
17	F	180,000	9	25	24	26	+	0	0	--	0	0	0
18	M	240,000	3+	>25	26	28	+	+	+	--	+	—	+
19	F	250,000	14	1	14	15	+	+	0	--	+	0	0
20	M	>100,000	16	12	23	30	+	+	0	--	+	+	+
21	F	240,000	13	4	10	17	+	+	+	--	0	+	0
22	F	30,000 60,000	6½	Birth	6	6½	+	+	+	--	0	+	0
23	F	480,000	6½	½	2	9	+	+	+	--	0	0	0
24	F	240,000	12	24	33	36	+	+	?	--	0	+	0
25	F	150,000	7	17	18	24	+	+	0	--	+	+	+
26	M	300,000	27	1	23	28	+	+	0	--	+	0	0
27	M	240,000	7	13	20	20	0	+	0	--	+	0	+
Older children													
1	M	200,000	5½ yr.	5 mo. ?	6 yr.	6 yr.	+	+	0	--	0	+	0
2	F	347,340	6 wk.	6 yr.	4 yr.	4 yr.	+	+	0	--	+	+	+
3	F	300,000	2 yr.	2 yr.	14 yr.	14 yr.	+	+	+	--	+	+	+
Adults			10	13 yr.							+	+	+
1	F	600,000	16	42½ yr.	42½ yr.	44 yr.	+	+	0	+	+	+	+
2	M	240,000	2	26 yr.	26 yr.	28 yr.	+	+	0	--	+	+	+
3	F	150,000	4 yr.	46 yr.	46 yr.	52 yr.	+	+	0	--	+	+	+
4	F	240,000	8½ yr.	19½ yr.	21 yr.	28 yr.	+	+	+	+	+	+	+
5	M	60,000	3 yr.	51 yr.	52 yr.	54 yr.	0	+	+	--	0	0	0
6	F	240,000	7	21 yr.	21 yr.	21 yr.	+	0	0	--	+	0	+

* Normal, 40 to 160 U. S. P. or International units per 100 ml.
† Normal, 17 μg. to 41 μg. per 100 ml.
‡ Normal, 10 to 20 Lowe units per 100 ml.

Chronic Vitamin A Intoxication

Skin Lesions	Loose Hair	Fissured Lips	Bleeding	Vit. A Level/100 Ml.	Bone X-Ray Changes	Enlarged Liver	Enlarged Spleen	Alk. Phosphatase, Bod. U.	Author
0	+	0	+	910 U. S. P. units °	+	+	+	+	Josephs °
+	+	+	+	254 μg. †	+	+	0	(18.7) †	Toomey & Morlarotte °
+	+	0	0	943 I. U. °	+	+	0	+ (17)	Dickey & Bradley °
+	+	+	0	2081 I. U.	+	+	0	+ (11.9)	Rothman & Leon °
+	+	+	?	660 I. U.	+	+	0	N (8)	Rothman & Leon °
0	0	+	0	--	+	0	--	+ (18)	Caffey °
0	0	+	0	830 I. U.	+	0	--	--	Caffey °
+	0	0	0	1364 I. U.	+	0	--	+ (13)	Caffey °
0	0	0	0	--	+	0	--	+ (19)	Caffey °
0	0	0	0	1306 I. U.	+	+	--	N (9.7)	Caffey °
+	0	0	0	--	+	0	0	--	Caffey °
+	+	--	--	--	+	+	--	+ (22)	Caffey °
+	0	0	0	1030 I. U.	+	+	0	+ (14.9)	Berry °
+	0	0	±	2000 I. U.	+	+	0	+ (25)	Fried & Grand °
+	0	+	0	127 μg.	+	--	--	N (7.7)	Fried & Grand °
0	0	0	0	--	+	--	--	--	Wyatt et al. °
+	+	+	0	1040 I. U.	+	0	0	--	Rineberg & Gross °
+	0	0	0	230 I. U.	+	0	0	--	Batz °°
+	+	+	0	837 μg.	+	+	--	N (12)	Cl. Case 622 °°
0	+	0	+	--	+	0	0	+ (16.3)	Gribets et al. °°
0	0	0	0	287 μg.	+	+	0	+ (17.9)	Gribets et al. °°
0	+	0	0	1121 I. U.	+	+	--	N (9.4)	Arena et al. °°
+	+	+	+	2670 I. U.	+	0	0	N (7.5)	Nas & Edwards °°
+	0	0	0	100 blue U.S	+	+	--	N (6.8)	Reyerbach et al. °°
+	0	+	0	"4+ elevated"	+	+	0	--	Goldzier et al. °°
0	±	0	? (Anemia)	672 μg.	+	0	0	N (2 K. A.)	Harrison & Mercer °° Tudor °°
+	+	+	0	480 I. U.	0	+	+	+	Pickup °°
+	+	+	+	700 I. U.	0	+	—	+ (25)	Pickup °°
+	+	+	0	707 I. U.	0	0	0	0 (10)	Oliver
+	+	+	0	--	0	0	0	0 (2.5)	Sulzberger & Lazar °°
+	+	+	0	227 μg.	0	+	0	N (7)	Shaw & Nicholl °°
+	+	+	+	2000 μg.	0	0	0	--	Bifulco °°
0	0	0	0	--	+	+	+	N	Gerber et al. °°
+	0	+	6+ Ouabio	69 μg.	0	+	0	+	Bloch °°
			0	832 μg.	0	+	0	N (2.2 K. A.)	Elliott & Dryer °°

body. Coarsening of the skin often precedes the eruption. Desquamation, particularly of the palms and soles, as noted in the present case, is commonly observed. Fissuring and scaling of the lips and looseness of the hair leading to alopecia have been observed in all of the older children, in the majority of adults, and in about one-third of the infants and toddlers. The eyebrows and the axillary and pubic hair may also be involved. Before looseness occurs, it is frequently noted that the hair becomes dry and coarse. Liver enlargement has occurred in approximately one-half of the cases. Liver-function tests, when performed, have been normal.

Central nervous system involvement has not been a common manifestation, but, as demonstrated in the present case, it constitutes an important sign. The signs and symptoms are the result of elevation of cerebral spinal fluid pressure. Abrupt rise in CSF pressure with attendant symptoms of headache, nausea, vomiting, and vertigo are the most prominent symptoms in acute intoxication with vitamin A. These symptoms have been described in adults since as early as 1597, when the symptoms were described by Gerritt de Veer[26] following the ingestion of polar bear liver. Other polar explorers subsequently have reported similar symptoms which have clearly been demonstrated to be due to the high concentration of vitamin A in the livers of many polar animals.[27] In children, as well as adults, acute vitamin A intoxication is characterized by central nervous system involvement. Marie and Sée[28] observed four children less than 12 months of age, three of whom ingested a single dose of 300,000 to 350,000 units of vitamin A or a vitamin A and D preparation. Toxicity emerged in the fourth infant after a similar total dose, but this was given over a six-day period in the form of nose drops. The authors demonstrated that the effects were due to vitamin A alone and not to the combination of A and D by giving 350,000 units of vitamin A to six additional infants, three of whom developed acute hydrocephalus. Symptoms and signs of increased spinal fluid pressure occurred within 24 hours and were manifested by projectile vomiting, tense and bulging fontanel, irritability, restlessness, insomnia, and drowsiness. Except for an increase in intracranial pressure there was no abnormality of the cerebral spinal fluid, and symptoms subsided within 48 hours. The most striking example of central nervous system involvement among the cases of chronic hypervitaminosis A is that of a 28-year-old woman reported by Gerber.[22] Seven years prior to diagnosis she developed headache, nausea, and diplopia and was noted to have nystagmus, strabismus, and papilledema. Spinal fluid pressure was increased. Ventriculograms were normal. A subtemporal decompression was performed, and the area remained bulging and tense for seven years, during which time the patient continued to ingest excessive amounts of vitamin A. Prior to the correct diagnosis, neurologic diagnoses included brain tumor, encephalitis, and chronic meningitis. The increased intracranial pressure promptly subsided when vitamin A was discontinued. Hydrocephalus has occurred in three children less than 3 years of age with chronic hypervitaminosis A. One child with typical skin and bone changes of hypervitaminosis A had increased spinal fluid pressure and a subdural hematoma.[6] Whether the latter was associated with hypervitaminosis A is not known. In experimental animals with hypervitaminosis A bleeding into the subcutaneous tissues, around spontaneous fractures, in the brain, and in the viscera is a common finding. The mechanism is believed to be antagonism between excessive vitamin A and vitamin K, with resultant hypoprothrombinemia. It is not clear whether vitamin A interferes with absorption of vitamin K or with its action within the liver. In humans, bleeding has not been a prominent manifestation. In addition to the child with subdural hematoma, one patient had rather severe bleeding of the gums following dental extraction, which subsided coincident with the administration of vitamin K,[21] and

another had a severe he
tonsillectomy.[1] Unfortu
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Laboratory studies f
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case of hypercalcemia
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another had a severe hemorrhage following tonsillectomy.[2] Unfortunately, coagulation studies were not performed in either patient. Indeed, in only one instance has an abnormal prothrombin time been observed, and this was not a constant finding in that case. Children with hypervitaminosis A have frequently demonstrated minor epistaxes, but whether this is related to vitamin A intoxication or to the rather common occurrence in this age group is not known.

In the present case and in two of three adults hypomenorrhea has been observed, and in all cases the menstrual periods have promptly returned to normal after cessation of the medication. No other endocrine disturbances are reported, although there have been hints suggesting inhibition of thyroid function by vitamin A. It was for this reason that protein-bound iodine and basal metabolic rate were obtained in the present case, with normal results. In experimental animals antagonism between excess vitamin A and thyroxin appears to be quite well established.[29]

Laboratory studies for the most part are within the normal limits. Calcium and phosphorus metabolism is not altered, and no case of hypercalcemia has been described. This helps to rule out the consideration of vitamin D intoxication occurring concomitantly with hypervitaminosis A. This combination has never been reported, probably because the dose of vitamin D in the usual cod D preparations, such as percomorph liver oil, is not large enough to cause intoxication with vitamin D. In 12 of 21 infants and toddlers in whom an alkaline phosphatase determination was obtained the level was elevated beyond normal (greater than 13 Bodansky units).. In the two children described by Pickup there was striking elevation of the alkaline phosphatase, and in one adult, the patient with ligamentous calcification, the alkaline phosphatase was elevated on occasion.

The mechanisms whereby prolonged administration of vitamin A causes toxicity remain unknown. This subject has recently been excellently reviewed by Nieman and Klein Obbink.[29] In laboratory animals Wolbach has demonstrated that the skeletal changes are due to acceleration of the epiphyseal cartilage sequences, absorption of bone, and appositional bone growth. These changes are in conformity to normal bone pattern. Linear growth in animals is normal or may be impeded, but it is never accelerated. Fractures often occur in animals and can be explained by the extensive loss of previously formed cortical bone before the newly formed bone has acquired firmness sufficient enough to meet mechanical requirements.[26]

The cause of increased cerebral spinal fluid pressure is entirely mysterious. Most authors believe that the increase is due to excessive production of cerebral spinal fluid. However, there is little experimental evidence for this. Of interest, increased intracranial pressure has also been described in vitamin A deficiency, both in laboratory animals[31] and, more recently, in children.[32] Similarly, increased intracranial pressure has been described in hypophosphatasia[33] and following oxytetracycline, chlortetracycline, and tetracycline therapy.[34,35] Whether there is a common mechanism in these clinically unrelated conditions is not known.

The most important differential diagnosis in the infant and toddler age group is a consideration of infantile cortical hyperostosis (Caffey's disease).[36] Both hypervitaminosis A and Caffey's disease share as common manifestations bone pain, soft tissue swelling, irritability, and x-ray changes. In the past it has been emphasized that the differential diagnosis could be made on the basis of age—infantile cortical hyperostosis occurring before one year of age and hypervitaminosis A after one year. That this is not the case is demonstrated in Figure 6. In 6 of the 27 infants and toddlers the onset of symptoms was before 12 months of age; in 4 of the 6 the onset was before 6 months. The diagnosis was established in three of the six children before 1 year, but

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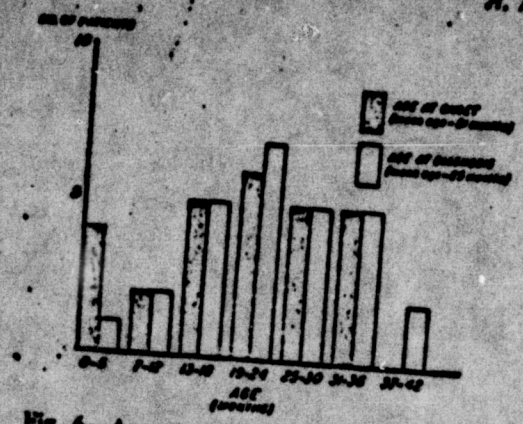

Fig. 6.—Age at onset and diagnosis of hypervitaminosis A in the infant-toddler age group. Note that six children (22%) had the onset before one year of age. There is little delay between onset and diagnosis in this age group (see also fig. 8).

in only one was it made before 6 months. While age does not serve in the differential diagnosis of these two diseases, there are other differences which separate the two. In Caffey's disease there is often fever, an elevated white blood cell count and a rapid erythrocyte sedimentation rate. The distribution of bone lesions is another important differential point. The mandible, which is commonly a site of involvement in infantile cortical hyperostosis, has never been involved in a reported case of hypervitaminosis A. Cutaneous manifestations, which are common in vitamin A poisoning, are not an accompaniment of Caffey's disease. Finally, the diagnosis of hypervitaminosis A is established by the high vitamin A level in the serum.

The interval between initiation of the toxic dose and the onset of symptoms is shown in Figure 7. In more than half of the infants the interval was between 1 and 12 months. In only 2 of the total of 36 cases did symptoms occur in less than one month after the initiation of the high dose. Of interest, but not of significance, because of the small numbers in each sample, the average interval in both infants and adults from the onset of the toxic dose to symptoms was 10 months. It is clear that there is a latent period between the onset of high-dose therapy and the emergence of toxic symptoms. Many factors may be responsible for this delay, including individual variations in absorption, utilization, and excretion. One factor that appears established is that the liver must become saturated with vitamin A before symptoms arise. The excessive accumulation of vitamin A in the liver is believed to be responsible for the hepatomegaly which has been observed in more than half of the reported cases.

Once the symptoms have arisen, the interval before the diagnosis is established varies in the different age groups (Fig. 8). In the infant and toddler groups the diagnosis was established in all except 1 child

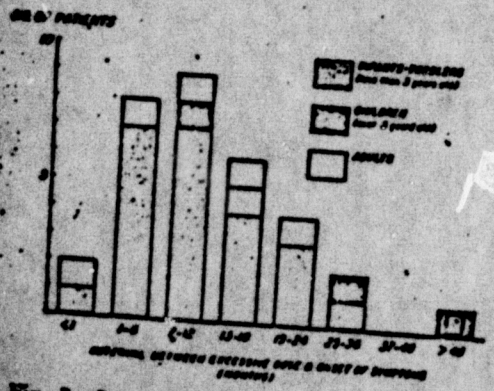

Fig. 7.—In all age groups there is a definite latent period between the initiation of excessive vitamin A intake and the emergence of symptoms of intoxication. The average interval is 10 months.

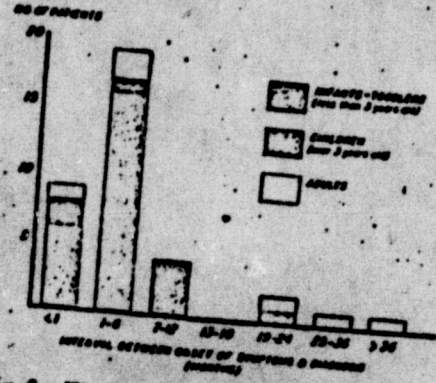

Fig. 8.—The interval between the onset of symptoms and diagnosis of hypervitaminosis A. In most infants (and all three older children) the diagnosis was made within six months of the onset of symptoms. In half of the adult group there was considerable delay before the diagnosis was considered.

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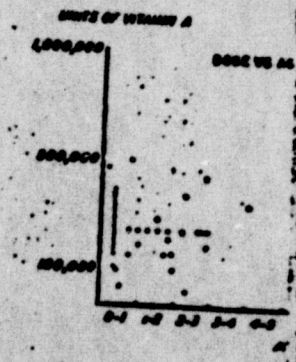

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by 12 months after the onset of symptoms and in 22 of the 27 within 6 months of the onset. In the three older children the diagnosis was established equally early, namely, within one month in two children and in my case two months after the onset of symptoms. However, in half of the six cases occurring in adults there was a considerable delay in the diagnosis, the longest being seven years. The reason for this appears to be that the manifestations of hypervitaminosis A, particularly the x-ray changes, permit rapid recognition in infancy, but in adults (and probably in older children, as more cases are described) without x-ray changes delay occurs until this diagnosis is entertained on other grounds.

The minimum toxic dose in man is not known. It has been estimated by Caffey that in children 1 to 3 years of age 100,000 units daily will result in chronic intoxication after a latent period of at least six months. There is no apparent relationship between age and dose, as can be seen in Figure 9. It can be seen that in four children and one adult toxicity occurred with the dosage of 100,000 units per day or less. The toxic dose in experimental animals has been reviewed by Nieman and Klein Obbink. There is considerable variation from species to species. Most of the work has been done in rats, and in this animal there is definite relationship of dose to age, younger animals being more susceptible. Few studies of chronic toxicity have been performed in humans. Josephs gave 500,000 units daily to an 8-month-old infant for four months without rise in fasting vitamin A level in the serum or emergence of symptoms. He also gave 200,000 units daily to two infants for "several weeks" without symptoms but with temporary rise in the serum vitamin A level lasting for one week. It is apparent from the paucity of cases, on the one hand, and the extensive use of vitamin A in large doses, on the other, there is great variation in the handling of vitamin A by individual persons, but most are able to excrete the medication rapidly enough to prevent accumulation. It also must be pointed out that none of the various carotinoids cause symptoms of hypervitaminosis A.[37] While large doses of β-carotene will result in yellow coloration of the skin (carotenemia) no other manifestations occur. The reasons for this appear to include the observations that carotene is less readily absorbed than vitamin A and that conversion into vitamin A is not rapid enough to allow accumulations of toxic quantities of vitamin A.

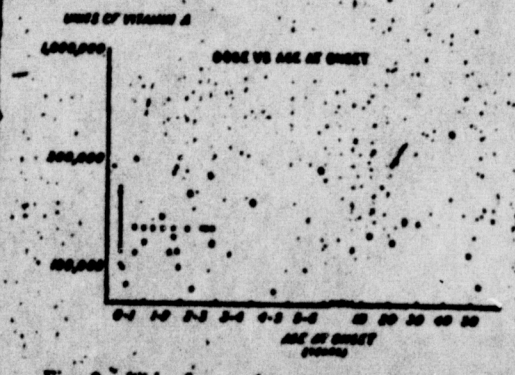

Fig. 9.—This figure demonstrates that there is no relationship between the dosage of vitamin A and the age of the patient. The frequency of dosage of 200,000 to 300,000 units in the infant-toddler age range is a reflection of the common usage of approximately 1 teaspoonful (4.9 ml.) of percomorph liver oil daily resulting in toxicity.

No therapeutic measures are indicated in chronic vitamin A intoxication. Withdrawal of the agent invariably results in prompt disappearance of symptoms. There are no prolonged sequelae of the disorder once the medicament is discontinued.

The recommended daily dose of vitamin A is 1500 I. U. in children up to 1 year, 2000 units from ages 2 to 3 years, 2500 units from 4 to 6 years, 3500 units from 7 to 9 years, and thereafter and in adults 5000 units per day except increasing to 6000 during pregnancy and 8000 units during lactation.[37-39]

In persons with biliary obstruction or steatorrhea vitamin A is poorly absorbed, because it is fat-soluble, and deficiency may ensue. Also, in cirrhosis of the liver vitamin A storage may be impaired. Therefore,

in these situations larger doses, up to 20,000 units daily, are indicated. Vitamin A administration in the recommended dosage will prevent the clinical manifestations of hypovitaminosis A, which include night blindness, xeropthalmia, and keratomalacia and, less importantly, skin changes, including follicular hyperkeratosis. As mentioned previously, increased intracranial pressure may also occur with hypovitaminosis A in infancy.

The indications for vitamin A administration in dermatologic diseases are not established. Some texts do not mention the use of vitamin A, while others suggest its use in conditions where there is excessive keratinization, either diffuse, as in icthyosis, or limited to the follicular system, as in acne vulgaris. For example, one text states "the dermatologic dose of vitamin A is 100,000 units per day, although in some disorders up to 300,000 units per day are required and treatment must be continued for a period of months to achieve the desired effect".[40] In general, dermatologic texts provide either very scanty or no information to the reader regarding vitamin A intoxication.[41-44] One commonly used textbook of medicine states that ". . . doses [of vitamin A] up to 300,000 units per day for a number of months have not produced detectable harmful effects. . . ."[45] The implication that such dosages are without risk is not consistent with the facts presented here. It is recognized that vitamin A in large doses is often prescribed by dermatologists. The extremely low incidence of chronic intoxication indicates that most persons can tolerate such doses. However, this does not justify its use, particularly when its value in skin disease is questionable. If prescribed for a "clinical trial," present evidence suggests that the dose should not exceed 50,000 units daily for a period of not more than two months.

Finally, in terms of better understanding the epidemiology of vitamin A intoxication, it is of interest to examine the reported cases for responsibility of prescribing the toxic dose. In 25 of the 27 cases among infants the family was responsible. In these situations the mother usually gave more than the prescribed dose because "it would do more good." In two of the infants the responsibility appeared to be with the physician, who in one instance prescribed high doses of vitamins for the diet and in the other, because of a large fontanel. Examination of the nine cases in older children and adults revealed that in seven of the nine cases the intoxication must be considered iatrogenic. In all of the older children vitamin A had been prescribed for skin conditions. This was also true in four of the six adults. In the present case some responsibility must also be placed with the patients, who did not discontinue therapy when this was recommended, although there was clear evidence of vitamin A intoxication before that time. In one adult advertising claims must be held as the responsible factor. Coupled with the claims of irresponsible firms are the facts that vitamin A in large amounts may be purchased without prescription over the druggists' counter or by mail, and, of even greater importance, I was unable to find indication on any label of vitamin A preparations that toxicity with large doses or prolonged administration might occur.

Summary

A case of chronic hypervitaminosis A in a 14-year-old girl is presented, and the English literature, comprising 36 cases in infants and toddlers, children, and adults, is reviewed.

The symptoms, signs, and laboratory findings are discussed. In general, all age groups share common symptoms and signs. X-ray changes of the long bones occurred in 100% of infants and toddlers but in only one of nine persons in the older groups. Central nervous system symptoms and signs due to increased intracranial pressure occurred in 20% of the total group.

All manifestations of hypervitaminosis A subside promptly following withdrawal of vitamin A. No sequelae were observed.

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Age at onset does not serve as an absolute differential diagnostic point between hypervitaminosis A and infantile cortical hyperostosis. Six of twenty-seven infants and toddlers with hypervitaminosis A had the onset of symptoms before one year of age.

A latent period (averaging 10 months) between the initiation of excessive dosage of vitamin A and the emergence of symptoms is characteristic.

The normal daily requirement of vitamin A in all age groups is given. Except in situations of impaired fat absorption, the recommended daily dose should not be exceeded.

The value of vitamin A in large doses in certain skin diseases is questionable. A clinical dermatologic trial of vitamin A should not exceed 50,000 units daily for longer than one or two months. In 9 of the 36 cases of hypervitaminosis A an excessive dose of vitamin A had been prescribed by a physician.

Vitamin manufacturers should include a warning of possible intoxication due to excess dosage on the labels of vitamin A preparations. This is not the practice at the present time.

The retinal photograph was made by Drs. William Havener and Jack H. Prince, Department of Ophthalmology, The Ohio State University.

The Children's Hospital, 17th St. at Livingston Ave. (5).

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Gargoylism

A Review Includ

ENID F. GILBERT, M.B.B.S., an

Gargoylism was first re in 1917, but it was not u that the disease was de detail by Hurler.[2] Clinic characterized by skeletal facial features, mental re ment of the liver and sp of the corneas. When a are present, the disease nized. However, those c of the characteristic crit as formes frustes.

The purpose of this p five cases, two of whic Negro children. The lat be the first documented goylism in the American tion, a review of the li made, as well as a summ advances in the recognitic ing of the fundamental c case process.

Report of C

CASE 1.—A 4-year-old Ne on Jan. 21, 1954, because of and abdomen for one day. admission he had developed infection. The patient was was thought to be a seven r birth weight being 2665 gm. family history was not cont with support at 7 months, v and at 4 years could speak c

The physical examination a dwarfed 4½-year-old Negr

Received for publication Ju Aug. 7.

From the Department of Hospital; formerly Fellow Gilbert, present address, Ass sociate Pathologist (Dr. Ga pital, Washington, D. C.

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Strabismus
Marshall M. Parks

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Eye Manifestations of Chronic Vitamin A Intoxication

THOMAS E. OLIVER Jr., M.D., and WILLIAM H. HAVENER, M.D., Columbus, Ohio

Poisoning due to prolonged ingestion of large amounts of vitamin A occurs primarily in children receiving excessive vitamin dosage. Occasional cases are seen in adults because of the very high level of vitamin A used in some disorders. Apparently on an empirical basis, 1000 to 500,000 I. U. daily have been advised in treatment or prophylaxis of the common cold, acne, a variety of dermatoses with particular selection of those exhibiting hyperkeratosis, ocular diseases manifesting themselves by night blindness or corneal degeneration, and sometimes in otologic, gynecologic, renal, and enteric disorders. Indications for such use of vitamin A are not clearly established, and serious doubt exists as to the value of this type of treatment. Since 5000 to 7000 I. U. are recommended as the minimum daily requirement for adults, it is apparent that a very wide range exists between actual need and toxic levels of vitamin A.

Manifestations of vitamin A toxicity do not appear until many months of a fairly high dosage. (Enormous single doses may cause an acute rise in cerebrospinal fluid pressure, with attendant symptoms of headache, vomiting, and vertigo. These symptoms may be noted when single doses as high as 350,000 units are given an infant. Apparently shark and polar bear liver contain high concentrations of vitamin A, and acute intoxications are reported following a single meal of these livers.) Toxic symptoms include the central nervous system manifestations of increased intracranial pressure; exophthalmos; loss of hair, cutaneous rash, desquamation, and pigmentation; migrating arthritis pains, bleeding,

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Ohio State University, Department of Pediatrics (Dr. Oliver) and Acting Chairman, Department of Ophthalmology (Dr. Havener).

Fig. 1.—Incidence of symptoms in 36 cases summariz[illegible] by Oliver.

hyponenorrhea; hepatomegaly and splenomegaly, and generalized malaise (Fig. 1).

Although not a common manifestation, central nervous system involvement is the feaure of vitamin A intoxication most likely to result in ophthalmologic consultation. The cause of increased intracranial pressure is unknown, though most authors believe it to be due to increased secretion of cerebrospinal fluid. The patient may have a typical papilledema, accompanied by the usual headaches, and sometimes develops extraocular muscle paralyses with diplopia. (Gerber reports a young woman taking 500,000 units of vitamin A daily for treatment of a skin disorder. During a period of eight and one-half years she was hospitalized 10 times in five different institutions, with diagnosis of subtentorial tumor, serous meningitis, chronic encephalitis, and infectious arthritis. Subtemporal decompression, tantalum cranioplasty, and repeated ventriculograms were done. She became totally disabled from hypertrophic arthritis and manifested all the other symptoms of vitamin A intoxication, which improved dramatically when vitamin A was stopped.) Infants may show bulging fon-

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tanelles and other manifestations of internal hydrocephalus, including increased digital markings of cranial bones.

Exophthalmos is occasionally present but is not marked. It is best detected by persons familiar with the patient's previous appearance. Clinical studies of orbital tissue are not available. Speculation as to cause of this exophthalmos should take into account the known antithyroid activity of very large doses of vitamin A. Animal experimentation has clearly established this inhibitory activity. Reported limitations of extraocular movement have been on the basis of nerve paralysis rather than orbital infiltration.

Loss of hair is generalized and includes the brows and lashes. Desquamation may be marked, especially affecting the palms and soles. Often a diffuse cutaneous pigmentation develops. An itching maculopapular eruption may spread over the entire body.

The commonest manifestation of vitamin A intoxication is migrating pain and tenderness of the bones (noted in 34 of the 36 cases surveyed by Oliver). In infants this pain is often associated with noninflammatory swelling overlying the long bones. Characteristic roetgenologic findings of cortical hyperostosis and mottling are seen in children. Adults rarely show positive x-ray findings. The spontaneous fractures reported in laboratory rats do not occur in human cases.

Hypoprothrombinemia, which responds to vitamin K therapy, may cause bleeding following minor injuries or surgery. Adult females develop hypomenorrhea, which disappears promptly when vitamin A is discontinued. Hepatomegaly and splenomegaly may occur. General irritability, anorexia, and weight loss are common.

Treament of vitamin A intoxication is entirely dependent upon the recognition of the syndrome and withdrawal of vitamin A therapy. Symptoms clear spontaneously within a short period of time.

The following report describes a typical case of hypervitaminosis A.

A 14-year-old white girl was admitted [illegible] Children's Hospital on Sept. 11, 1950, [illegible] the chief complaint of leg pain of [illegible] weeks' duration. Two years prior to [illegible] mission the patient developed superficial nonpitting acne vulgaris, for which, [illegible] months prior to admission, 200,000 units [illegible] vitamin A daily had been prescribed by a dermatologist. Two months prior to admission she had her last normal menstrual period, succeeding ones being at the normal interval but scanty and of one day's duration. About the same time, the patient noted scaling and cracking of her lips and fissures at the corners of her mouth, for which she used a number of salves without success. Five weeks before admission she began complaining of dull constant pain in both legs, particularly about the knees, aggravated by activity. At this time she was seen by her private physician, who directed that vitamin A be discontinued. This advice was not heeded by the patient, unbeknownst to either her family or the physician. In the month prior to admission leg pain worsened. She walked with a noticeable limp, favoring her left leg, and was unable to continue gym activities. She observed that her scalp hair became dry in texture and fell out in large quantities with brushing. She also developed a maculopapular eruption on the trunk and desquamation of palms and soles. The family observed during this period that she manifested increasing irritability, but there were no specific symptoms of central nervous system involvement. No bleeding or bruising was noted. Appetite remained good, although the patient was on a self-imposed rather rigid diet because of the acne.

Family history was noncontributory.

Past history was essentially unremarkable. Menarche occurred two and one-half years prior to admission, and menstrual periods had been normal up to the present illness.

Physical examination. Weight, 54 kg.; height, 169 cm.; blood pressure, 130/70. Skin. The face was the site of superficial

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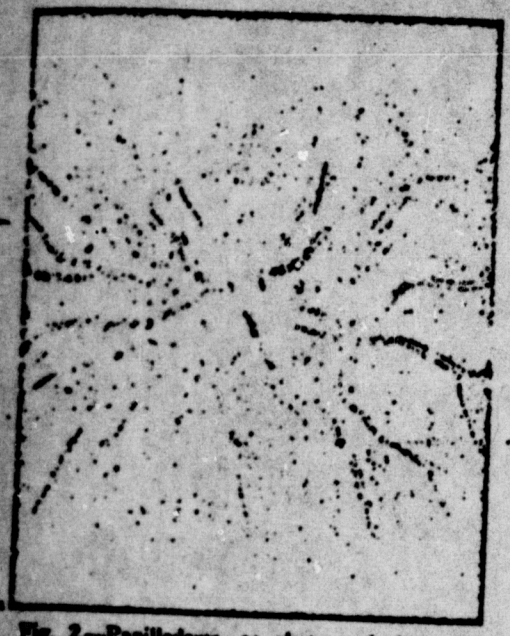

Fig. 2.—Papilledema, as photographed at time of diagnosis of our case.

nonpitting acne vulgaris and milia. The lips were scaled and cracked, and there were fissures at the corners of the mouth. Over the trunk and to a less degree on the extremities was a fine discrete light-tan nonpruritic papular eruption. The skin was dry, and the palms and soles were desquamating in sheets. The underlying skin in these areas was delicate and thin. Nikolsky's sign was absent. The scalp hair was dry and loose. There was moderate alopecia. Pubic and axillary hair was normal. As seen in Figure 2, the typical appearance of early papilledema was present in each eye. The disc margins were completely blurred and slightly elevated, and the physiologic depression was obscured. Slight venous engorgement existed, and spontaneous venous pulsation was absent. Minimal external pressure elicited venous collapse. Fine capillary dilation was apparent on the disc surface. Glistening retinal edema encircled the disc, extending out about 1 dd. A number of fairly large and dense flame-shaped hemorrhages were clustered about the disc. The macula and periphery were completely normal. There were no visual symptoms. External ocular examination was entirely negative. (Specifically, no exophthalmos or extraocular muscle paresis existed.) Abdomen. Liver and spleen were not enlarged. Extremities: Pain and tenderness in both legs, more on the left, particularly medial and inferior to the tibial tubercle. There was no swelling, heat, or redness. There was no weakness, sensory disturbance, or reflex changes, nor were there signs of meningeal irritation. Mentation was normal to bedside testing.

Laboratory data. Hemoglobin, 12.9 gm/100 ml.; white cell count, 8050 per cubic millimeter, with a normal differential count; platelets, normal on appearance; blood urea nitrogen, 24 mg/100 ml.; CO_2, 21 mEq/liter; chloride, 102 mEq/liter; total base, 149 mEq/liter; total protein, 7.3 gm/100 ml.; albumin, 3.6 gm.; globulin, 3.7 gm/100 ml.; calcium, 10 mg/100 ml.; inorganic phosphate, 3.5 mg/100 ml.; alkaline phosphatase, 3.5 Bodansky units; cephalin flocculation, 1+; thymol turbidity, normal; cholesterol, 94 mg/100 ml.; protein-bound iodine, 9.6μg/100 ml. (Sept. 20, 1956); repeat, 4.8μg/100 ml. (Oct. 25, 1956). B. M. R., normal. Skeletal survey including long bones, spine, and skull, normal. Lumbar puncture (supine), crystal-clear fluid; initial pressure, 600 mm. H_2O; cells, 3 per cubic millimeter; sugar and protein, normal. EEG, normal. Fasting serum carotene and xanthophyll (Sept. 11, 1956), 264μg/100 ml. (normal, 75μg. to 150μg.) and 135μg/100 ml. (normal, 40μg. to 80 μg.), respectively; on Feb. 4, 1957, 195μg/100

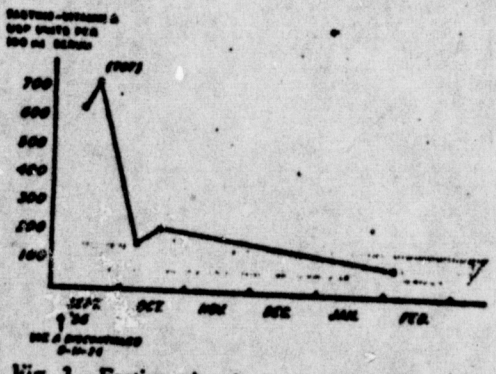

Fig. 3.—Fasting vitamin A levels. Shaded area indicates normal range.

ml. and 98 μg/100 ml., respectively. The fasting vitamin A levels are shown in Figure 3.

Course. A diagnosis of chronic hypervitaminosis A was made on admission, and all medications were discontinued. Symptoms and signs began to abate within a week, and the patient was entirely asymptomatic, except for continued loose hair, after two weeks. She was discharged on Sept. 17, 1956. When examined on Oct. 6, 1956, there were no abnormalities, except that alopecia and superficial acne vulgaris (unchanged from before) were noted. Ophthalmoscopic examination was entirely normal, with no residue of the retinal hemorrhages. Regrowth of scalp hair, which was of fine texture, was not observed until six weeks after the vitamin A was stopped. Menstrual periods became normal in duration two months after medication was stopped. The patient has remained asymptomatic for nine months.

Summary

The syndrome of chronic vitamin A intoxication includes the central nervous system manifestations of increased intracranial pressure, mild exophthalmos, loss of hair including brows and lashes, cutaneous eruptions and pigmentation, migrating arthritic pains, hypoprothrombinemia, hepatomegaly and splenomegaly, hypomenorrhea, and generalized malaise.

A case of chronic hypervitaminosis A in a 14-year-old girl is presented.

The vitamin A levels were determined by Gilbert Forbes, M.D., Rochester University School of Medicine and Dentistry.

Dr. Sophie Rogers gave permission to report this case, and Prof. Jack Prince did the retinal photography.

University Hospital (10).

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Summary

An analysis of the recent experience with subacute thyroiditis at the Hitchcock Clinic shows that there is good reason to believe that the disease is more common than our statistics would indicate. The diagnosis may be overlooked and the patient treated for pharyngitis, or some similar condition, while the thyroiditis runs its clinical course. It seems probable that some patients simply do not report the symptoms to a physician when the disease is not particularly severe.

The major reasons for delay in diagnosis were either failure to consider the possibility of thyroiditis or failure to palpate the thyroid gland. The management of symptomatic treatment is relatively satisfactory. Patients with mild cases may need only aspirin, but generally the more severe symptoms require specific medication, such as with adrenal steroids, or x-ray therapy. The response to steroid therapy is dramatic.

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VITAMIN A INTOXICATION AS A CAUSE OF PSEUDOTUMOR CEREBRI

George Morrice Jr., M.D., William H. Havener, M.D.

and

Frederick Kapetansky, M.D., Columbus, Ohio

Three girls aged 14, 15, and 16 years had diplopia, papilledema, and other symptoms suggesting brain tumor. In addition to various individual complaints, each had hypomenorrhea, alopecia, and rhagades or other marked forms of dermatosis. They had been taking, respectively, 200,000, 200,000, and 90,000 units of vitamin A per day. Treatment consisted in stopping the intake of vitamin A; in addition the oldest patient received acetazolamide as a diuretic. The symptoms subsided rapidly, but in the oldest patient slight blurring of the margins of the optic disks were still present six months later. Alopecia, rhagades, nonspecific dermatitis, migratory arthralgia, hepatosplenomegaly, and hypomenorrhea are important in the differential diagnosis between the pseudotumor cerebri of chronic vitamin A intoxication and true intracranial tumor.

Pseudotumor cerebri is a syndrome of uncertain and probably multiple etiology. It presents the picture of increased intracranial pressure with headache and papilledema. Localizing neurological signs such as extraocular muscle palsies are most uncommon. Complete neurosurgical diagnostic procedures are clearly indicated to rule out brain tumor, but their results are negative in pseudotumor cerebri. The increased intracranial pressure is self limited, of some months' duration, and causes little damage, except that, in untreated severe cases, the patient may go blind from optic atrophy. Although subtemporal decompression effectively reduces pressure, this surgical therapy has been superseded by acetazolamide (Diamox) therapy. Acetazolamide, in doses of 500 mg. twice daily, will ordinarily bring intracranial pressure within normal limits. The highest incidence of pseudotumor cerebri is in adolescent or young adult females, usually those who are overweight.[1]

Recognition of chronic vitamin A intoxication as a cause of the pseudotumor cerebri syndrome is im-

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portant, because withdrawal of the excess vitamin A cures the patient; also expensive, uncomfortable, and hazardous neurosurgical diagnostic procedures may be avoided. Diagnosis of chronic vitamin A intoxication is simple, providing the physician is aware of the syndrome. In all cases of pseudotumor cerebri the patient and her family should be carefully questioned, as the vitamin administration may have been suggested by friends or a druggist and not prescribed by a physician. After some months of daily ingestion of 100,000 units or more, the patient develops dryness, roughness, and desquamation of the skin; fissuring of the angles of the lips; loss of hair; migratory bone pain; hypomenorrhea; palpable enlargement of liver and spleen; and increased intracranial pressure. Naturally, the presence of the findings and their severity is subject to considerable variation, depending on individual susceptibility and the amount of vitamin A intake. A typical papilledema develops and is opthalmoscopically indistinguishable from the papilledema of brain tumor.[3] Great emphasis must be placed on the fact that the papilledema may not disappear for from four to six months after vitamin A is discontinued. Unless the physician realizes this, his confidence is shaken in advising against arteriographic and pneumoencephalographic examination. Presumably, this persistence of papilledema is related to the large amounts of vitamin A that are stored in the liver.

At times, large doses of vitamin A have been urged for skin, eye, renal, gynecologic, and ear disorders as well as the common cold. The recommended daily requirement of vitamin A is 5,000 units in adults, increased to 6,000 units a day during pregnancy and 8,000 during lactation. Vitamin A in large doses is prescribed most commonly by dermatologists for acne vulgaris, although such use rests on only empirical grounds. Oliver[3] has suggested that if vitamin A is used at all in treatment of skin disease, a clinical trial should extend not more than two months, at a dosage which does not exceed 50,000 units daily, and labels on vitamin A products should include a warning of possible intoxication due to excess dosage. Case histories of three patients with vitamin A intoxication follow.

Report of Cases

Case 1.—A 14-year-old girl was admitted to Children's Hospital on Sept. 11, 1956, with the chief complaint of leg pain of five weeks' duration. Two years prior to admission, the patient developed superficial nonpitting acne vulgaris, for which, 10 months prior to admission, 200,000 units of vitamin A daily had been prescribed by a dermatologist. Two months prior to admission she had her last normal menstrual period, succeeding ones occurring at the normal interval but scanty and of one day's duration. About the same time the patient noted scaling and cracking of her lips and fissuring at the corners of her mouth, for which she used a number of salves without success. Five weeks before admission, she began complaining of dull constant pain in her legs, particularly about the knees, which was aggravated by activity. At this time she was seen by her private physician, who directed that vitamin A be discontinued. This advice was not heeded by the patient, unknown to either her family or the physician. In the month prior to admission, leg pain worsened. She walked with a noticeable limp, favoring her left leg, and was unable to continue in gymnastic activities at school. She observed that her scalp hair became dry in texture and fell out in large quantities with brushing. A maculopapular eruption on her trunk and desquamation of her palms and soles developed. The family observed during this period that she manifested increasing irritability, but there were no specific symptoms of central nervous system involvement. No bleeding or bruising was noted. Appetite remained good, although the patient was on a self-imposed, rather rigid diet because of the acne.

Family history was noncontributory. The patient's own history was essentially unremarkable. Menarche occurred two and one-half years prior to admission, and menstrual periods had been normal up to the present illness.

Physical Examination.—Her weight was 54 kg. (129 lb.); height, 169 cm. (5 ft. 5 in.); and blood pressure, 130/70 mm. Hg. The face was the site of superficial nonpitting acne vulgaris and milia. The lips were scaled and cracked, and there were fissures at the corners of the mouth. Over the trunk and, to a lesser degree, on the extremities was a fine discrete light-tan nonpruritic papular eruption. The skin was dry, and the palms and soles were desquamating. The underlying skin in these areas was delicate and thin. Nikolsky's sign was absent. The scalp hair was dry and loose and there was moderate alopecia. The pubic and axillary hair was normal. As seen in figure 1, the typical appearance of early papilledema was present in each eye. The disk margins were completely blurred and slightly elevated, and the physiological depression was obscured. Slight venous pulsation was present. Minimal external pressure elicited venous collapse. Fine capillary dilatation was apparent on the disk surface. Glistening retinal edema encircled the disk, extending out about 1 disk diameter. A number of fairly large and dense flame-shaped hemorrhages were clustered about the disk. The macula lutea and periphery were completely normal. There were no visual symptoms. External ocular examination was entirely negative. (Specifically, no exophthalmos or extraocular muscle paresis existed.)

The liver and spleen were not enlarged. Pain and tenderness existed in both legs, more in the left, particularly medial and inferior to the tibial tubercle. There was no swelling, heat, or redness. There was no weakness, sensory disturbance, or re-

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flex changes, nor were there signs of meningeal irritation. Mental functions were normal to bedside testing.

Laboratory Data.—Hemoglobin level was 12.9 Gm. per 100 ml.; white blood cell count, 8,050 per cubic millimeter, with a normal differential count; platelets, normal in appearance; blood urea nitrogen level, 24 mg. per 100 ml.; carbon dioxide level, 21 mEq. per liter; chloride level, 102 mEq. per liter; total base, 149 mEq. per liter; total protein level, 7.3 Gm. per 100 ml., with 3.6 Gm. of albumin and 3.7 Gm. of globulin per 100 ml.; calcium level, 10

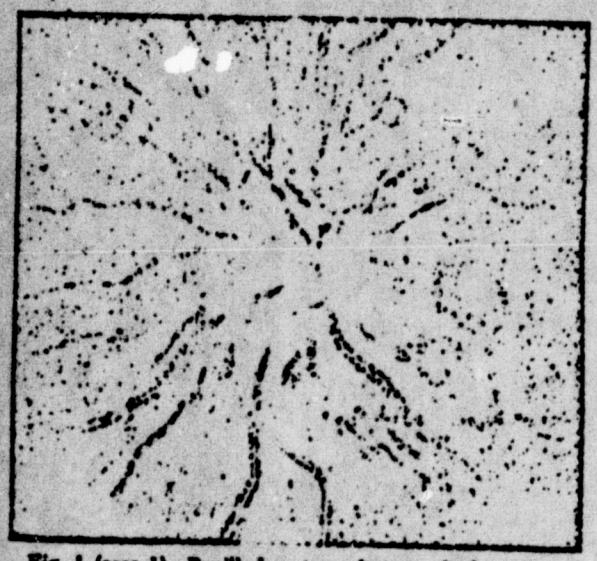

Fig. 1 (case 1).—Papilledema, as photographed at time of diagnosis.

mg. per 100 ml.; inorganic phosphate level, 3.5 mg. per 100 ml.; alkaline phosphatase, 3.5 Bodansky units; cephalin flocculation, 1+; thymol turbidity, normal; cholesterol level, 94 mg. per 100 ml.; protein-bound iodine level, 9.6 mcg. per 100 ml. (Sept. 20, 1956), repeat value, 4.8 mcg. per 100 ml. (Oct. 25, 1956); and basal metabolic rate, normal. The skeletal survey, including long bones, spine, and skull, showed normal findings. Lumbar puncture (supine) showed crystal-clear fluid; initial pressure, 600 mm. H_2O, with 3 cells per cubic millimeter and normal sugar and protein levels. Electroencephalographic findings were normal. Fasting serum carotene and xanthophyll levels (Sept. 11, 1956) were 264 mcg. (normal, 75 to 150 mcg.) per 100 ml. and 135 mcg. (normal, 40 to 80 mcg.) per 100 ml., respectively; on Feb. 4, 1957, 195 and 98 mcg. per 100 ml., respectively. The fasting vitamin A levels are shown in figure 2.

Course.—A diagnosis of chronic hypervitaminosis A was made on admission, and all medicaments were discontinued. Symptoms and signs began to abate within a week, and the patient was entirely asymptomatic after two weeks, except for continued loose hair. She was discharged from hospital on Sept. 17, 1956. When examined on Oct. 6, 1956, no abnormalities were seen except alopecia and superficial acne vulgaris, unchanged from before. Ophthalmoscopic examination showed entirely normal findings, with no residue of the retinal hemorrhages. Regrowth of scalp hair, which was of fine texture, was not observed until six weeks after the vitamin A therapy was stopped. The patient had remained asymptomatic for nine months to the time of writing.

Case 2.—A 16-year-old girl was admitted to University Hospital on March 11, 1959, with the chief complaint of double vision for from five to six weeks prior to her admission. For the past three and one-half to four years, she had been taking 90,000 units of vitamin A daily for her acne. Since the acne would regress during the summer months, she tended to decrease or even abstain from medication during the hot months. During the fall, prior to her admission to the hospital, she noted for the first time that her legs and hands were covered with red, scaling lesions. Also, there were fissures at the corners of her mouth and her lips scaled continually. She further noted more than the usual amount of falling hair during this time. For the six weeks prior to admission, she noted persistent horizontal diplopia. She had a complete physical examination by her family doctor who suggested that the vitamin A injection might be the cause of her symptoms,

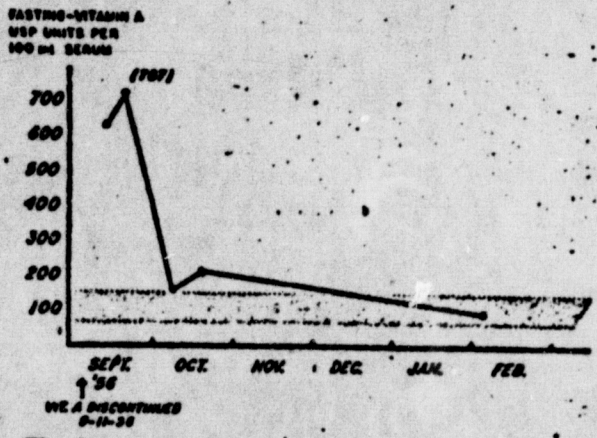

Fig. 2 (case 1).—Fasting vitamin A levels. Shaded area indicates normal range.

and requested that she discontinue its use. She did so without any immediate symptomatic relief and was admitted to the hospital for further study.

The patient had become increasingly irritable during the past year but denied specific central nervous system symptoms. She had lost 14 lb. during the previous year but had been on a self-imposed rigid diet. She denied easy bruising or bleeding. Her previously normal menstrual periods had become irregular, with only scanty flow.

Physical Examination.—She weighed 57 kg. (125 lb.); height, 160 cm. (5 ft. 7 in.); blood pressure, 122/80 mm. Hg. The skin of the upper cheeks and forehead had several small pits from previous acne

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vulgaris. The lips were scaled and cracked. In the corners of the mouth, there were small fissures. The skin was dry, and there was fine dry scaling over the forearms, hands, and feet. Scalp and pubic hair were normal. The optic disks bilaterally showed slight elevation with blurred margins. The veins were slightly dilated and spontaneous venous pulsation was absent. There was capillary dilation on the surface of the disk and a linear hemorrhage just off the disk of the left eye. The retina surrounding the disk was glistening and edematous for from ½ to 1 disk diameter distance. The macula lutea and periphery were normal. The external eye examination was negative. No abdominal organs were palpable. No bone pain or tenderness was present.

Laboratory Data.—Hematocrit determination was 40%; white blood cell count, 4,300 per cubic millimeter, with a normal differential count; platelets, normal on smear; urine, normal on voided specimen; alkaline phosphatase level, 10.29 Bodansky units; electroencephalographic findings, normal; and fractional pneumoencephalographic findings, normal. The bone survey included normal findings of chest, hands, and feet. The skull showed minimal separation of the suture lines. Lumbar puncture showed crystal-clear fluid; opening pressure was 50 to 70 mm. H_2O (after pneumoencephalographic examination), with 21 lymphocytes per cubic millimeter and normal protein and sugar levels. Visual fields showed enlarged blind spots.

Course.—On treatment with diuretics, the patient noted immediate improvement in visual complaints and lost seven pounds of weight. Papilledema persisted unchanged for several months and then gradually decreased. Slight blurring of the disk margins was still present on Aug. 11, 1959.

Case 3.—A 15-year-old girl, on May 15, 1958, noted some chapping of her arms, with cracking and peeling of her lips, as well as some ankle joint stiffness. On the weekend of June 6, she slept continuously and was somnolent for the next two days. On June 8, she had diplopia, and the next day she had headache, ringing in her ears, nausea, and anorexia. She was examined by Dr. J. E. Edwards of Lancaster, Ohio, on June 11, with findings of splenomegaly and bilateral papilledema. He suspected vitamin A poisoning because of her somnolence, anorexia, and peeling of the skin, so inquiry was made as to the possible intake of this vitamin.

It was learned that she had initially been given vitamin A, 50,000 units a day, by her druggist, which was later increased to 200,000 units per day by a dermatologist. Her skin was reported to have cleared considerably with this therapy.

Dr. Edwards discontinued therapy with vitamin A and referred her to a local ophthalmologist who, because of the papilledema and retinal hemorrhages, wished her to have neurosurgical investigation. By June 30, her appetite had improved and she was no longer sleepy or readily fatigued. Diplopia persisted. There had been no change in her menstrual periods. When asked, her mother commented that hair had come out in handfuls on recent washing.

On examination, there was found an alert, quiet girl of stated age who weighed 57 kg. (125 lb.). Her hair was soft, fine-textured, and markedly thinned on the forehead and over the ears. There were pitted acne scars of the face, and the remainder of the skin was dry, scaly, and thickened. She had bilateral papilledema, with scattered perivascular linear hemorrhages. In the right retina there was a sharp white patch of exudate. Cardiovascular examination was normal with a blood pressure of 120/80 mm. Hg. The spleen was palpable three finger-breadths below the left costal margin, non-tender, and firm. Neurological examination was normal, including angiographic and pneumoencephalographic examination.

Her red blood cell count was 4,720,000, with a platelet count of 330,900 and a coagulation time of nine minutes. The alkaline phosphatase level was 2.9 Bodansky units and acid phosphatase level 0.1 Shinowara-Jones-Reinhart units. The serum calcium level was 10.0 mg., and the serum phosphorus level was 2.5 mg. The carotene blood level was 38.8 (normal 10 to 20) Blue units per 100 ml. Serum electrophoretic pattern was completely normal.

The therapy consisted of stopping the vitamin A medication. The diplopia disappeared on July 2, but the papilledema did not completely subside until Sept. 9, 1958.

Summary

Chronic vitamin A intoxication will produce a syndrome consistent with the diagnosis of pseudotumor cerebri. Diagnosis is made by the associated presence of typical skin disorder, hair loss, hepatomegaly and splenomegaly, bone pain, somnolence, mental irritability, anorexia, diplopia, and hypomenorrhea. Papilledema due to chronic vitamin A intoxication may require some months to disappear. The use in skin diseases of vitamin A in large doses over many months is questioned, and any patient receiving such medication should be carefully observed for toxicity.

310 W. 10th Ave. (10) (Dr. Havener).

Doctor George Stine granted permission for the report of one case.

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RESEARCH AND REFERENCE BRANCH

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Acute and chronic hypervitaminosis in a 4-month-old infant

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ALBUQUERQUE, N. MEX.

THE purpose of this paper is to report the case of a 4-month-old infant with clinical manifestations of acute and chronic forms of hypervitaminosis A. We believe this to be the youngest infant with manifestations considered to be those of the chronic form of the disease.

Hypervitaminosis A has been diagnosed with increasing frequency since Joseph's[1] original description in 1944, and several reviews of the literature have appeared.[2-6] Caffey[2] pointed out that the minimal observed preclinical latent period of the chronic form was 6 months and that the longest was 13 months; the length of the latent period did not appear to depend on the size of the overdose.

Vitamin A intoxication has been observed in acute and chronic forms. Marie and See[3] first drew attention to acute poisoning in the infant following the administration of very large quantities of vitamin A to 4 infants, aged 3½ months, 7½ months, 3 months, and 4 months, respectively. The clinical patterns were usually characterized by the acute onset of hydrocephalus with intensive bulging of the fontanel, frequent vomiting, and agitation or insomnia without meningeal signs or other systemic complaints. The disturbance began within 12 hours after ingestion of approximately 300,000 units of vitamin A in each case. Symptoms in the acute form subsided rapidly and dramatically after cessation of administration of vitamin A, usually within 24 hours, even though the serum vitamin A level remained high.

The chronic form of hypervitaminosis A is characterized by an insidious onset with constitutional symptoms.[6] The manifestations include anorexia, dry itchy skin, alopecia with sparse, coarse hair, angular fissures or cracking of the lips, hepatosplenomegaly, and tender subcutaneous swellings over the long bones and skull. Cortical thickening of the long bones is usual after vitamin A has been given in excess for 6 to 15 months. An erythematous rash has been described.

Rathbun and Knudson[4] report that

CASE REPORT

First admission. This 2-month-old Caucasian male was born after an uneventful gestation period and normal delivery. Birth weight was 8 pounds. The neonatal period and subsequent course of the patient were uneventful until 2 months of age.

The infant was given Similac powder, 1:2 for the first month, then Varamel, 1:1. Solids were introduced at 1 month and at 2 months of age, 3 solid meals and 4 bottles of formula were being given. Through misinterpretation of the pediatrician's instructions, Trivisol, 8.4 c.c. had been given daily since the fourth day of life. The total vitamin A ingested was 70,000 units from the vitamin preparation plus that in the prepared formulas, at least 71,500 units daily.

Past and family histories were essentially noncontributory. The mother was 18 years of age and in good health; the father was 20 years old, living and well. A paternal great-aunt had tuberculosis, and the mother had experienced hematuria on one occasion in childhood.

At 2 months of age the mother noted bulging of the infant's anterior fontanel with no other symptoms except irritability. A pediatrician confirmed the presence of the bulging fontanel. Subdural and lumbar taps were performed, but the only abnormality noted was increased intracranial pressure. Chemical values of the spinal fluid were within normal limits. Brain tumor, encephalitis, or hydrocephalus was suspected. The patient was then sent from an outlying district to Albuquerque, New Mexico, for consultation.

Physical examination failed to show a bulging fontanel after a lumbar puncture. Hospital admission orders did not include vitamins.

X-rays of the skull revealed the calvarium to be symmetrical and average in dimension for a 2-month-old infant. There was no evidence of increased intracranial pressure

peared to be normally open. intracranial calcifications were ventriculogram detected "mi right and left lateral ventricles normal in contour and positio pression was "consistent with atrophy." Because of the suspi destruction, surgical explorati formed at the site of the bon abnormality of the bone or du The latter was opened, disclosi mality of the brain or leptomer

After one week of hospitaliza tient was asymptomatic and wa

At home, the excessive dose was again resumed. The infa clinically well until approximat later when "a lump" was notec side of the head directly above the right ear. This was bony in and nontender. Scalp hair was f patches, marked irritability was the infant slept less than usual. prior to the second admission, i that picking the infant up by elicited pain, as did any pronat tion, or abduction of the right of 101° F. was noted. Two d admission bulging of the ante occurred and repeated projecti was observed for the first time. readmitted for further studies.

Second admission. Physical disclosed a well-developed child of age. The infant was very i lethargic. Temporal subcutaneo bilaterally were present. Scalp patchy in distribution with areas Finger- and toenails were intact mal consistency. There was mar tabes. The anterior fontanel wa bulging, giving the appearance room. A tympanitic note was el percussion of the head. The spl palpable, but hepatomegaly extra

Fig. 1. At 2 months of age a defect was present in the midline of the skull through the parietal bone which was believed to represent a developmental variant (persistent parietal sagittal fontanel). There was no radiographic evidence of increased intracranial pressure.

over the right. No other bony abnormalities

normal chemistry determinations with the exception of protein 30 mg. per cent.

X-rays of the chest revealed subperiosteal new bone formation about the mid-third of both clavicles. Films of the cervical spine, mandible, and both lower extremities, including the feet, revealed no abnormalities. Re-examination of the skull showed that the irregular defect in the posterior parietal bone, noted 5 weeks previously, had been somewhat widened by operation but was otherwise unchanged in appearance. There was a small soft tissue bulge through the site of the defect.

Progress. Vitamins were not given in the hospital. The patient became afebrile without medication and gradually became more alert. A proprietary formula containing vitamins was ordered on admission but discontinued when the diagnosis was suspected. Two days after admission the patient was moving both arms fairly well. He continued to improve dramatically and was discharged on the fourth hospital day.

Fig. 3. Child at 4 months of age. Spotty alopecia with mushroom effect from increased intracranial pressure was observed.

skull failed to reveal the previously described defect and the clavicles were again normal.

DISCUSSION

Caffey[3] in his original paper describes the difficulty in differentiating infantile cortical hyperostosis and hypervitaminosis A. He points out that there are two features com-

outline by bring diagnosed clinical the first 4 months of life and by th of metatarsal lesions on x-ray exa In addition, bony lesions of the sl never been described in hypervitam At first admission to the hospital, the chest showed the clavicles wer in appearance. On subsequent adı weeks later, cortical hyperostoses w along the mid-third of the shafts clavicles consistent with that des chronic vitamin A poisoning. Altho tered soft tissue swellings were see time, a skeletal survey showed no a hyperostosis. Re-examination 5 mon when the patient was clinically well the clavicles had returned to norma ance.

At the original hospitalization a cm. defect was present through bo of the parietal bone in the midl scalp was flat over this defect, and t no radiographic evidence of increas cranial pressure. Surgical explora

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20 per cent.

Toomey and Morissette[8] performed the crucial experiment by feeding their patient excess vitamin A to reproduce the clinical picture of hypervitaminosis A. In other experimental studies involving humans, Marie and See[3] found that many of the clinical features of hypervitaminosis A disappeared when excessive vitamin A intake was stopped but promptly reappeared when the excessive dose was readministered. The serum vitamin A level, after an initial sharp fall, remained elevated for weeks, tapering off slowly to normal levels. Prompt exacerbation of symptoms is apparently possible with reingestion of excessive vitamin A before the saturated liver stores are depleted. This holds true with pure vitamin A as well as with fish liver oil concentrates.

The intriguing but unknown cause of increased cerebrospinal fluid pressure occurring in the acute form is particularly interesting. Although the mechanism is unknown, Bass[9] suggests that excess formation of spinal fluid occurs. Equally mysterious are indications of similar increase in cerebrospinal fluid pressure with certain tetracycline derivatives, and there are reports[10] that the same phenomena may result from avitaminosis A in humans.

SUMMARY AND CONCLUSIONS

1. This case report deals with what we believe to be the youngest patient with hypervitaminosis A. The diagnosis was made at 4 months of age, but clinical manifestations were present at 2 months of age.

2. The patient had symptoms and signs of both the acute and chronic forms of the disease at 4 months, characterized by increased intracranial pressure, bulging fontanel, tender subcutaneous swellings, and spotty alopecia. Discontinuation of vitamin A intake was followed by prompt improvement. Exacerbation of all the symptoms followed resumption of the excessive dose of vitamin A, the symptoms again cleared promptly upon discontinuing the vitamin A.

3. Skull lesions were present in this case and probably represent a coincidental developmental variant. The possibility that the lesions are related to hypervitaminosis A is mentioned.

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Congenital bile duct stenosis

Intrahepatic cholangiocholecystojejunostomy (Roux Y) with removal of intrahepatic stones

James D. Hardy, M.D., F.A.C.S.*

JACKSON, MISS.

ATRESIA of the extrahepatic bile ducts of congenital origin constitutes a largely unsolved problem in the newborn infant. Although occasionally the point of occlusion lies sufficiently distal to permit successful anastomosis of the proximal biliary tract to the alimentary tract, all too frequently the point of occlusion involves the right and left hepatic ducts and even the ducts within the liver itself. When this high level of obstruction is encountered, the surgeon has little choice but to close the abdomen. Nevertheless, some of these infants with bile duct atresia live for weeks or months and rarely a patient may live even longer. It is possible that very occasionally a patient may live long enough to permit the dilatation of intrahepatic bile ducts sufficiently to permit anastomosis of such a duct to the alimentary tract.

The present report deals with a case of congenital stenosis of the bile ducts involving both the right and left hepatic ducts. The patient, intermittently jaundiced from b reached the age of 14 years before seven tacks of pain with cholangitis and jaur necessitated exploratory operation with e tual anastomosis of a dilated branch of right hepatic duct to the alimentary through the intermediary gall bladder. I venous cholangiography preoperatively disclosed marked dilation of the intrahe bile ducts. At operation the biliary tr both lobes of the liver was filled by inje of radiopaque medium into a single br of the right hepatic duct. A large numb stones flowed from the branch of the hepatic duct as bile escaped under pres Many additional stones undoubtedly mained in the bile ducts throughout liver, emphasizing again the stasis fact biliary stone formation and especially i presence of intermittent infection.

From the Department of Surgery and University Hospital, University of Mississippi Medical Center, Jackson, Miss.

Aided by National Institutes of Health Grant

CASE REPORT

D. D., a 14-year-old Negro boy, wa admitted to the University Hospital on 15, 1959, with the complaint of jaundice ciated with pain in the right upper qua of the abdomen and fever. In essence, h had intermittent attacks of such sym since birth, and in fact he had been in

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Dr. Donald N. Adler, resident in obstetrics and gynecology at Harbor Hospital, for collaboration in the studies of umbilical-cord blood and placentas.

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VITAMIN A INTOXICATION IN ADULTS

Report of a Case with a Summary of the Literature

Seen adult case

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PREVIOUS summaries have considered the symptoms of vitamin A excess in children and adults together. Most of them have been published in pediatric journals. Because of the striking uniformity of the major symptoms in adults it seems worth while to analyze them alone even though only 6 cases have previously been reported. Although the symptoms are quite troubling to the patient they are often so mundane that the physician does not readily pursue them to a diagnosis. It is hoped that with broader awareness the phenomenon may be recognized earlier and its future occurrence prevented. Two distinct types exist, acute and chronic. The acute, which is usually due to a large single dose, is self-limited and results in spontaneous recovery. The chronic may be unrecognized for years. Cases summarized here were all of the chronic type.

Case Report

On January 5, 1960, a 32-year-old homemaker, a former nurse, was referred to the Clinic in Internal Medicine at the United States Public Health Service Hospital with a puzzling picture of intermittent abdominal pain and tenderness, anorexia, nausea, easy fatigability, low-back, right-hip and tibial pain, hepatosplenomegaly and leukopenia.

In May, 1958, she had been seen at this hospital because of the onset of nausea and right-lower-quadrant pain and tenderness. The white-cell count was 7100, and she was thought to have subsiding acute appendicitis. Two weeks later she was again seen with the same symptoms and a feverish feeling. The temperature was 99.6°F. The right lower quadrant of the abdomen was tender, with slight guarding but no rebound tenderness. The white-cell count was 4900, with a normal differential. A plain film of the abdomen and a gall-bladder series were normal. About 1 year later she was seen because of epigastric and subcostal discomfort, which tended to migrate to the right lower quadrant of the abdomen. In addition, she had noted malaise and easy fatigability and had acquired the habit of taking afternoon naps. Mild anorexia had caused her to omit occasional meals. Again right-lower-quadrant tenderness was present. The spleen had become palpable just below the left costal margin. The white-cell count was 3200, with 5 per cent band forms, 47 per cent neutrophils, 33 per cent lymphocytes, 9 per cent monocytes, 5 per cent eosinophils and 1 per cent basophils. Abdominal symptoms and signs subsided over the next few days, but malaise and lethargy persisted. In September, 1959, mild aching developed in the right sacroiliac and hip regions. In December she returned because of urinary frequency and urgency and a sensation of pressure in the suprapubic area. The spleen and liver were readily palpable, and there was tenderness in the right lower quadrant of the abdomen. Urinalysis was negative. The white-cell count was 4500, with 3 per cent band forms, 38 per cent neutrophils, 54 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. The hemoglobin was 14 gm. per 100 ml., and the sedimentation rate (Westergren technic) 9 mm. in 1 hour. Two tests for L.E. cells were negative.

She specifically denied taking medication of any nature, including vitamins. Physical examination revealed a well

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developed and well nourished woman of about the stated age who appeared somewhat tired. The hair was sparse over the anterior central crown. The eyes were prominent, and on comparison with a picture taken 10 years previously she thought that they had become more prominent. Exophthalmometric readings were 18.5 mm., the upper limit of normal. Anterior and posterior cervical lymph nodes varied from 0.5 to 2 cm. across and were soft and freely movable. Mild tenderness in the right lower quadrant of the abdomen was elicited on deep palpation. The liver and spleen were palpable 3 cm. below the respective costal margins, and the liver was tender. Urinalysis, white-cell and differential counts, hemoglobin, hematocrit, sedimentation rate, platelets, sternal bone marrow, serum bilirubin, cephalin flocculation, thymol turbidity, bromsulfalein and serum albumin and globulin were all within normal limits. Heterophil-antibody agglutination was negative.

Three weeks later, on her 3d visit, the patient continued to complain of persistent lethargy and lack of interest in her daily activities. She continued to note dull pain in the right hip and sacroiliac regions, and pain and tenderness had developed in the right clavicle. She stated that her husband thought that she should tell me she had been taking vitamin A for 3 years. One hundred thousand units daily had originally been prescribed by a dermatologist for acne. She had continued it without prescription, at first somewhat irregularly but daily for the 2 years before being seen in January, 1960. On direct questioning she thought that her hair had been coming out rapidly. She had noted frequent bouts of painful lumps on the margin of the tongue, and the lips had required creams and lipstick to keep them moist.

original literature. It has often been necessary to take slight liberties with the various authors' words to group the findings more readily, but an attempt has been made to avoid a change in meaning. Table 1 identifies and lists the basic facts of each case. It will be noted that the smallest dose to produce symptoms was 50,000 units of vitamin A daily for eighteen months. Some larger doses caused symptoms earlier, but there was always a latent period before they developed. Partial relief, particularly of general and musculoskeletal symptoms, was very prompt in all cases upon withdrawal of vitamin A. Essentially complete recovery occurred in all cases in a matter of months.

Table 2 lists the symptoms in the 7 cases of chronic vitamin A intoxication in adults. Totals have been listed to show the relative occurrence in this small group. Future experience may significantly alter some of these. As one can see, the list has been deliberately inclusive because of the present state of ignorance. Nevertheless, certain features are relatively constant and warrant further discussion.

TABLE 1. *Cases of Hypervitaminosis Thus Far Reported.*

Case No.	Source of Data	Age	Sex	Reason for Medication	Daily Dose	Duration of Medication	Duration of Treatment before Chief Symptoms	Interval between Withdrawal & Relief
		yr.			I.U.			days
1	Salzberger & Lamm[1]	44	F	Radio advertisement for dry thirsty & colds	600,000	16 mo.	12 mo.	90
2	Shaw & Nassau[2]	25	M	Not stated	275,000	2 mo.	6 wk.	9
3	Bideau[3]	32	F	Dry, fissured skin	100,000	4 yr.	12 mo.	7
4	Gerbac et al.[4]	28	F	Ichthyosis	300,000	8 yr.	7.5 mo.	17
5	Bloch[5]	34	M	Eczema of legs	50,000	3 yr.	18 mo.	7
6	Elliott & Dyer[6]	21	F	Acne	>150,000	7 mo.	3 mo.	60
7	Present report	32	F	Acne	170,000	5 yr.	3½ yr.	3

The liver was palpable 5 cm. below the right costal margin, and the tip of the spleen was also palpable. Tenderness was still present in the right lower quadrant of the abdomen. Percussion over the right tibia produced tenderness. The serum vitamin A level was 250 I.U. (normal, 50 to 200 I.U.). The serum calcium, phosphorus and alkaline phosphatase were normal. X-ray films of the long bones were normal.

Vitamin A was abruptly stopped, and within 3 days the patient noted marked improvement and no longer required daily naps. She felt renewed interest in her activities. The hip and back pain disappeared. She continued to note mild subcostal discomfort for 6 weeks. At that time the liver was still palpable at the right costal margin, but the spleen could no longer be felt. The white-cell count had returned to normal. Three months after stopping vitamin A she felt entirely well. The liver and spleen were palpable. The lips no longer required special care for dryness. The serum vitamin A had fallen to 104 I.U. She was still feeling entirely well 7 months after stopping vitamin A and had noted none of her previous symptoms. The liver was palpable 4 cm. below the right costal margin. Exophthalmometric readings were 18 mm. in both eyes — no change from those while on vitamin A.

Compilation of Cases and Discussion of Symptoms and Signs

All cases retain the same numbers throughout Tables 1-3 so that one may readily refer to the

General symptoms were present in all patients, but by far the most significant in frequency and severity was a feeling of fatigue. Some patients found it necessary to take daily naps to permit them to perform their tasks whereas others were eventually forced to give up their chores entirely. Lack of interest in surroundings was described in 2 cases and was implied in others. Women frequently noted shortening or cessation of the menstrual flow.

All patients had musculoskeletal symptoms, usually manifested by dull bone or joint pain, with occasionally severe pain. Usually, they complained of low-back ache that sometimes prevented sleep. Joint pain and sometimes stiffness, with little or no evidence of inflammatory involvement, was prominent. Occasionally, the pain seemed to be in the long bones, especially those of the legs, and was often aggravated by percussion. Clavicular pain and tenderness were present in 1 case. One prominent feature of all musculoskeletal symptoms was their tendency to wax and wane, with occasional periods of complete cessation. X-ray changes were present in only 1 case and

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revealed calcification in the pericapsular, ligamentous, tendinous and subperiosteal tissues.

Most cases showed some change in the epithelial system. Loss of hair was most frequent and was often in 1 case. Although pruritus occurred in only 2 cases it was a prominent symptom.

Gastrointestinal symptoms of anorexia and weight loss were relatively mild but could usually be obtained

TABLE 2. *Symptoms and Signs.*

Systems & Symptoms or Signs Present	No. of Cases	Case No. 1	2	3	4	5	6	7
General:								
Fatigue	5		×	×		×	×	×
Insomnia	3			×	×		×	
Decreased menstruation	3	×		×	×			
Fever, mild	1					×		
Night sweats	1	×						
Musculoskeletal:								
Bone or joint pain	7	×	×	×	×	×	×	×
Bone tenderness	3		×				×	×
Intermittent pain	3	×					×	×
X-ray changes	1				×			
Epithelial:								
Loss of hair	5	×	×	×	×			×
Desquamation or fissuring of lips	4	×	×		×			×
Desquamation, generalized	4	×	×		×			
Pigmentation or rash	4	×	×	×	×		×	
Sore tongue or mouth	3		×		×		×	×
Pruritus	2	×			×			
Oily skin	2		×				×	
Dry skin	1	×						
Gastrointestinal:								
Anorexia	4		×	×	×			×
Weight loss	3		×	×	×			
Nausea	2				×			×
Polydipsia	1		×					
Abdominal pain	1							×
Vague symptoms	1					×		
Reticuloendothelial:								
Hepatomegaly	5		×		×	×	×	×
Splenomegaly	2				×			×
Lymph-node enlargement	1							×
Hematologic:								
Anemia	3		×	×	×			
Leukocytosis	2	×				×		
Hemorrhage	2			×		× ?		
Neutropenia	1							×
Genitourinary:								
Frequency	3				×		×	×
Urgency	2				×			×
Incontinence, enuresis, enuresis	1				×			
Polyuria	1		×					
Neurologic:								
Headache	3			×	×	×		
Diplopia, nystagmus, internal strabismus, choked disks	1				×			
Increased cerebrospinal-fluid pressure	1				×			
Eye:								
Proptosis	3	×		×				×
Irritation & bleeding	1			×				

preceded by dryness and difficulty in grooming. It was usually manifested by general thinning on the scalp, but in some cases there was also loss of eyebrows and lashes and general body hair, including axillary and pubic. Dryness of the lips, frequently with desquamation and fissuring, particularly at the angles, occurred in over half the cases. The mouth and margins of the tongue were sore in 3 cases, and 2 patients described blisters on the edge of the tongue. Generalized desquamation and often dusky pigmentation were common, and a rash was described either voluntarily or on questioning. Although it was present in only 1 case pain in the right upper and lower quadrants of the abdomen was an early and chief complaint, subsiding promptly on withdrawal of vitamin A.

Hepatomegaly was definite in 5 of the 7 cases and in 1 was variable from week to week. Splenomegaly was present in only 2 cases. Mild lymph-node enlargement was observed in 1 case and partially subsided after withdrawal of vitamin A.

Mild urinary frequency occurred in 3 and urgency in 2 cases and likewise subsided on withdrawal.

Except for 1 case neurologic symptoms were not prominent in adults, in contrast to children and infants. In adults the only frequent neurologic symptom was headache.

Hematologic findings were irregular. Mild anemia was found in 3 cases, leukocytosis in 2, and neutropenia in 1. Hemorrhage was a prominent symptom in 1 case and probably present in another.

headaches, dizziness, sluggishness, irritability and a strong desire to sleep coming on a few hours after ingestion. This is followed in a day or so by generalized peeling of the skin and full recovery.

Chronic toxicity in human beings, a much more recent phenomenon, depends upon concentrated vitamin preparations. In 1938 Clausen[9] pointed out much suggestive evidence of clinical toxicity in

TABLE 3. *Laboratory Findings.*

Case No.	Hemoglobin	Red-Cell Count	White-Cell Count	Calcium	Phosphorus	Alkaline Phosphatase	Serum Vitamin A*	Serum Lipids	Liver Function†
	gm./100 ml.	X10⁶	X10³	mg./100 ml.	mg./100 ml.	units	per 100 ml.	mg./100 ml.	
1	14.0	4.2	13.0	9.2	3.5	4 (Bodansky)	60 blue units	895	—
2	12.0	3.9	(Normal)	13.3	3.1	7‡	163 microgm.	—	Normal
3	10.5	3.5	6.9	—	—	—	—	—	—
4	81%	4.0	10.7	9.4	3.8	3.3 (Bodansky)	[illegible]	410	Normal
5	15.2	—	17.2	—	—	—	[illegible] microgm.‡	(29 units!)	Normal
6	14.6	4.4	7.5	—	—	2.2 (King-Armstrong)	[illegible] microgm.	602	Normal
7	14.0	5.2	9.2	11.0	4.1	5 (King-Armstrong)	230 I.U.	692	Normal

*1 microgm. equivalent to 3.3 *USP* or international units of vitamin A.
†Method not stated.
‡Performed 2 mo. after vitamin A stopped.

Prominence of the eyes, which was the one finding that did not regress on withdrawal of vitamin A, was found in 3 cases. Ulceroblepharitis, with bleeding, occurred in 1 case. Choked disks, diplopia and nystagmus were present in another.

Laboratory data are presented in Table 3. The only constant finding was elevation of the serum vitamin A, which in some cases was tremendous. There seems to be some positive correlation between the level and the severity of symptoms and also the length of time required to return to normal. Anemia has been mentioned. Since it is a common finding experimentally in animals it is probably related to the hypervitaminosis. Liver-function tests were within normal limits in all cases in which the liver was enlarged. Likewise, there was no abnormality of the bleeding, clotting or prothrombin time in the case with definite hemorrhage. Serum calcium, phosphorus and alkaline phosphatase were normal in all cases in which they were measured except for 1 case, in which the calcium was 13.3 mg. per 100 ml.

Discussion

It has been common knowledge among Arctic peoples that liver from certain Arctic animals, especially the polar bear, was poisonous. One of the earliest written descriptions of toxicity (1596) is cited by Nieman and Klein Obbink.[7] Rodahl and Moore,[8] in 1943, found polar-bear liver to contain from 13,000 to 18,000 I.U. of vitamin A per gram of wet tissue and were able to produce evidence of vitamin A toxicity in rats fed this. Symptoms of acute toxicity from a single dose are uniformly described as abdominal pain, nausea, vomiting, severe

human beings. Josephs[10] described the first clinical case in 1914 in a three-year-old child. Oliver[11] summarized 36 cases, 27 in young children and infants, 3 in older children and 6 in adults. Morrice and his associates[12] recently reported 3 cases in adolescents.

Numerous animal experiments have demonstrated the toxic effects of large doses of vitamin A (Moore[13] and Moore and Wang[14]). Nieman and Klein Obbink[7] have nicely summarized the toxic effects in animals. Cohlan[15,16] has shown that numerous congenital anomalies can be produced in the offspring of rats by administration of large doses of vitamin A.

Hillman[17] induced symptoms of poisoning in a forty-year-old physician on two occasions, using doses of approximately 1,000,000 units daily for fourteen and twenty-five days, respectively. These were remarkably similar to those in the 7 reported cases. Frey and Schoch,[18] in treating 9 patients for psoriasis with large doses of vitamin A, produced similar symptoms in 5. From the foregoing data it seems that there is reasonable experimental evidence that the symptoms found in the 7 clinical cases tabulated in this paper could all have been due to vitamin A toxicity. It is of interest, however, to note that the great majority of these symptoms are also present in vitamin A deficiency in animals, as tabulated by Moore.[13]

When one tries to explain the various symptoms one is immediately struck by the great lack of understanding of the actions of vitamin A. Nieman and Klein Obbink[7] suggest that excess of vitamin A may produce secondary hypovitaminoses by displacement. Knudson and Rothman[19] discuss clinicochemical correlation. Hepatomegaly is considered most probably

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due to large deposits of vitamin A in the liver.[7] It is of interest that Logan,[20] upon administration of 50,000 units of vitamin A to human beings for three weeks or more, reduced the I^{131} uptake. Still, none of these mechanisms are proved, and the literature is replete with contradictions.

Children and adolescents comprise the great majority of clinical cases of toxicity. They may have any of the manifestations of vitamin A intoxication seen in adults. They are much more apt to have increased intracranial pressure with concurrent neurologic signs and may even show bulging of the fontanels and papilledema. Bone changes are prominent, with swelling and tenderness over the long bones of the upper and lower extremities. In infants and toddlers x-ray study may reveal cortical hyperostosis, mottling or osteoporosis.

The adult daily requirement for optimum nutrition according to the National Research Council is 5000 units. During pregnancy and lactation the requirements are probably 50 per cent greater. Hume and Krebs[21] found that 1 male subject experimentally depleted of vitamin A gradually regained dark adaptation on 1300 units of vitamin A daily, but the blood level did not rise to normal until this was increased to 2600 units daily. As can be seen, there is real danger of toxicity from protracted use of large doses, and when one deviates from the officially recommended dose one must watch for this.

Summary

A case of chronic vitamin A intoxication in an adult is added to the 6 previously reported. All patients took at least 50,000 units of vitamin A daily for a protracted time. There was a latent period of weeks or months before the onset of symptoms somewhat inversely related to the size of the daily dose. Principal symptoms were bone or joint pain that tended to be intermittent, fatigue and insomnia, loss of hair, dryness and fissuring of the lips and other epithelial involvement, anorexia and weight loss and hepatomegaly. Several other symptoms regarded as probably due to vitamin A intoxication were less common. Relief was prompt and nearly complete on withdrawal of vitamin A. The only diagnostic laboratory finding was an elevation of the serum vitamin A. The literature is reviewed for its clinical application.

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Dermatologica 123: 293-300 (1961)

From the Dermatological Department of the Finsen Institute, Copenhagen
(Chief: Professor Poul V. Marcussen, M. D.)

Chronic Intoxication with Vitamin A in Adults

With Report of a Case

By W. RAASCHOU-NIELSEN

The toxic effect following the administration of large doses of vitamin A to animals has been recognized for some years, whereas a similar effect in man has been observed to only a limited extent. Joseph's original description in 1944 of chronic poisoning in a three-year-old child was followed during the next few years by several reports of clinical hypervitaminosis A in children, so that by 1958 a total of 30 well-documented cases had appeared [17].

Chronic intoxication in adults seems to be of a more sporadic nature. It was first described by *Salzberger and Lazar* in 1951, and a further 7 cases have been reported since then [2, 7, 9, 11, 23].

As concentrated preparations of vitamin A are easily available, and as it seems less well-known that prolonged ingestion of such preparations may be toxic for adults also, the possibility cannot be excluded that intoxication is more frequent than generally supposed.

Report of a case: On the 27th of April 1959, L. F., an 18-year-old woman, attended the dermatological out-patient's department for alopecia. Apart from a urinary tract infection of brief duration four years earlier, she had been in good health generally and menses regular, receiving among other medication synthetic ribenin A palmitate (Arovit "Roche") orally, in doses corresponding to 300,000 I. U. daily. However, she had stopped taking the preparation on her own accord five weeks before attending the clinic.

She had suffered from anorexia for the last four months, and her weight had fallen from 52 to 46 kg. which she herself ascribed to psychic stress. She was gaining in weight again.

During the last two months she had noticed increasing fall of scalp hair, which had at the same time become dry and brittle. The eyebrows and pubic hair had also thinned out. The skin felt dry and itchy, and she was troubled by scaling around the mouth and by fissures at the angles of the mouth and in the nostrils.

She had not felt tired or out of sorts, and had not noticed any nail changes, bone tenderness or arthralgia. Menstruation had been regular, of the usual degree and duration.

On physical examination she appeared healthy, colour Eph blood, moderately well-

nourished, weight 50.3 kg. Her facial skin was dry and scaling in patches, with acneiform infiltrations of the forehead and cheeks. Scattered excoriations from scratching were seen. Scaling and rhagades at angles of mouth were observed. The scalp was dry and showed fine scaling.

Hair growth was diffusely thinned out over the entire scalp. The hairs were stiff, sat in disorderly wisps and needed only a slight pull to come out. The eyebrows were light, thin and very sparse.

Axillary hair appeared to be normal, but the pubic hair was thinned out. The lanugo hair was retained on the trunk and extremities. The finger nails were of normal appearance.

There was no exophthalmos, vision was normal, and an ophthalmological examination showed nothing abnormal.

Conjunctiva and oral mucosa were normal. There was no goiter and no palpable enlargement of liver or spleen.

X-ray examination of the abdomen showed no enlargement of organs, and X-rays of spine, upper arm, lower arm and knee joint showed nothing abnormal.

The following laboratory studies were made: Hb 88%, erythrocyte count 4.0 million, E.S.R. 37 mm., white blood cell count 10,100 with normal differential count, prothrombin 78% (slightly reduced), coagulation time 4 mins.

Serum lipoids 910 mg. 100 ml., lipoid phosphorus 6.3 mg. 100 ml., neutral fat 487 mg. 100 ml. Total cholesterol 226 mg. 100 ml., cholesterol esters 181 mg. 100 ml. Protein-bound iodine 3.1 3.0 µg. 100 ml. Serum proteins: total value 8.4 g. 100 ml., albumin 5.4 g. 100 ml., globulin 3.0 g. 100ml. Serum calcium 9.8 10.0 mg. 100 ml., serum phosphorus 3.3 mg. 100 ml.

Alkaline phosphatase 3.0 3.2 units (*Bach and Bach*'s method, normal values 3–7 units).

The determination of total vitamin A in the plasma (done at the central laboratory, Bispebjerg hospital, according to a method described by *Ollendorf*) gave the following results at the dates indicated (normal value 50–150 I. U. per 100 ml. plasma:

1. 5. 1959: 733.6 I. U. per 100 ml. plasma
19. 5. 1959: 171 I. U. per 100 ml. plasma
1. 6. 1959: 121.6 I. U. per 100 ml. plasma
15. 6. 1959: 178.2 I. U. per 100 ml. plasma
30. 6. 1959: 150 I. U. per 100 ml. plasma
14. 7. 1959: 192 I. U. per 100 ml. plasma
4. 4. 1960: 72 I. U. per 100 ml. plasma

The symptoms were observed to disappear rapidly during the months following the first attendance. Weight was increasing, and the patient reported feeling in better health. After one month (seven weeks after stopping the vitamin A medication) it was observed that the hair was less wispy. After 1 ½ months a fresh growth of hair was observed on the vertex, and after 3 ½ months the entire scalp showed a pronounced crop of dense, strong, medium fair hair, about 3 cm. in length. The remains of the original growth could be seen at the same time, as scattered lighter hairs, about 10 cm. in length. The eyebrows were now thicker than before, and rather dark. The acneiform infiltrations on the face had disappeared.

Fig. 1a. 19/5/59
Marked loss of hair.
Hairs stiff, dry and unmanageable.

Fig. 1b. 14/11/59
Regrowth of normal scalp hairs.

Fig. 2a and 2b. Supercilia on 19.5.59 and 14/11/59.

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After six months the hair stand was of uniform length, and according to the patient, thicker in growth and darker in shade than before the vitamin A treatment started.

Discussion

The most important data from the 9 cases of chronic poisoning with vitamin A in adults are collected in Table I. Wherever the determination was made, the plasma vitamin A level showed elevated values, most often varying from 800 I. U. to 2,000 I. U. per 100 ml. Such elevated values begin to fall immediately after discontinuing the vitamin A therapy. The values measured, therefore, do not express the degree of intoxication directly, as in some cases the initial determination of the vitamin A content of the plasma was made before its consumption was stopped, in other cases at varying periods after this.

In the present patient, an elevated value was found although the determination was made five weeks after she stopped taking the vitamin. The subsequent analyses, made at intervals of two weeks, gave results which were normal or possibly slightly elevated. The latter is probably the case, as a determination made one year later gave a considerably lower level than the previous determinations.

The normal range is reported as being generally between 50 and 150 I. U. per 100 ml. of plasma (1 µg. = 3.3 I. U.) [3, 8, 12, 18]. However, others report a slightly higher level [16, 21].

The falling vitamin A content of the blood after stopping its administration in those experiencing intoxication from it, has been studied in only a few cases. *Gerber*, whose patient provided the highest recorded value of all (2000 µg. per 100 ml.), made daily determinations after discontinuing the medication, and found that the amount of total vitamin A (ester + alcohol fraction) fell strongly during the first two days, and then more slowly, so that the concentration was still elevated after two months (approx. 300 µg. per 100 ml.).

Oliver Jr. and Harvey observed the same rapid initial fall, followed by a slower approach to normal values in the course of 3–4 months.

Clinical Picture

The most prominent symptoms in this patient were dermatological, a characteristic of this form of chronic intoxication in adults. The widespread loss of hair, fissures of the lips, perlèche and the itchy, dry scaling skin were present in most of the patients. However, in some cases the skin changes seem to have been of a more seborrhoeic nature.

A macule-papular rash is described on the trunk [17, 23]. In some cases, loss of hair also included the lanugo hairs [11, 23, 24]. In several patients, widespread or localized pigmentation is seen.

General symptoms were observed in most cases. In this patient, loss of weight and anorexia may well have been caused by the intoxication, and they gave way to a rapid increase in weight when ingestion of the vitamin ceased. At the same time, the patient reported feeling in better health, although she had denied being generally affected when first examined.

On the other hand, the tendency to haemorrhage which is found in several cases [2, 7] was not observed. In agreement with this, the laboratory studies showed that the coagulability of the blood was unaffected. The haemorrhagic diathesis has been shown to be caused by hypoprothrombinaemia. However, the conditions are perhaps more complicated [14, 22, 25].

Disturbances of menstruation – usually in the form of hypomenorrhoea – were observed in several adult patients. In others, including a few of those apparently most severely intoxicated, menstruation was normal.

Bone tenderness was not noticed by this patient, but has appeared to a mild degree in some cases. This symptom dominates in chronically intoxicated infants, accompanied by swelling of the soft parts over the long bones and the metatarsals. *Caffey* has described the characteristic deposition of subperiostal hyperostoses, demonstrable by radiography.

Symptoms from the central nervous system, so general in cases of acute poisoning with vitamin A, and accompanied by increased intracranial pressure [1], were demonstrated in only one case of chronic poisoning in an adult [11].

The hepatomegaly which is found occasionally is usually interpreted as the result of the deposition of vitamin A in the liver.

Characteristically, normal concentrations of calcium and phosphorus in the blood were found in this patient, which fact is of value in deciding whether a simultaneous vitamin D intoxication may be present. Further, in contrast to children, adults usually show normal values of alkaline phosphatase.

The rapid remission after terminating intake of the vitamin is also a conspicuous feature of diagnostic value in the syndrome. In the present patient, this was especially pronounced for the hair-growth, and the increase in weight was also striking. According to *Breslau*, the

TABLE I

Symptoms and Signs in Nine Reported Cases of Chronic Vitamin A Intoxication in Adults

Case No.	Age at diagnosis, years	Sex	Vitamin A dose units	Dose duration months	Vitamin A level	Bone pain	Constitutional symptoms	C.N.S. symptoms	Menstrual disorder	Skin lesions	Loss of hair	Fissured lips	Bleeding	Hepatomegaly	Author
1	44	F	600,000	18	60 chloe units[a]	+	+	0	+	+	+	+	0	0	Sulzberger and Lazar
2	25	M	200,000	2	237 μg.[b]	+	+	0	-	+	+	+	0	+	Shaw and Nicoll
3	52	F	100,000	48		+	+	+	+	+	+	0	+	0	Bifulco
4	28	F	500,000	102	2000 μg.	+	+	+	0	+	+	+	0	+	Gerber et al.
5	21	F	160,000 180,000	7	832 μg.[c]	+	+	0	0	+	0	0	0	+	Elliot and Dryer
6	18	F	150,000	27		0	+	0	+	0	+	0	+	0	Creek et al.
7	49	M	200,000	28		0	0	0		0	0	0	+	0	Creek et al.
8	67	M	200,000	72		0	0	0		+	0	0	+	0	Creek et al.
9	18	F	300,000	18	20 μg.[d]	0	+	0	0	+	+	+	0	0	Rosenbaum-Nielsen

[a] One week after last intake of vitamin A preparation.
[b] One week after last intake of vitamin A preparation.
[c] Three days after last intake of vitamin A preparation.
[d] Five weeks after last intake of vitamin A preparation.

remission is manifest after 3–10 days with respect to anorexia, headache and pruritus. Tissue changes are in general reversible [11].

Toxicity

The minimum doses of vitamin A required for chronic intoxication are not known with certainty, and appear to be subject to great individual variations. They also depend of course on the duration of the period of intake. While acute intoxication develops following a single ingestion of several million I. U., the table shows that chronic intoxication in adults can develop after ingestion of smaller amounts over a longer period of time. *Sulzberger and Lazar*'s patient took 600,000 I. U.

for one year before symptoms were noticed. *Frey and Schoch* and *Miescher* treated skin patients with large doses of vitamin A and observed no side effects after daily ingestion of 400,000 I. U. for a period of 1–3 months.

On the other hand, *Bifulco*'s patient developed symptoms after ingesting 150,000 I. U. daily for one year. *Gerber* observed intoxication in a person taking amounts as relatively modest as 50,000 units of vitamin A daily for 8 months, and *Perdrup* made the same observation in a patient who took 200,000 I. U. for 3 months. In agreement with this, the *Council on Foods and Nutrition 1959* stresses that a daily intake of more than 25,000 units vitamin A should be followed closely with an eye to toxicity, and points out that there is a definite risk of dangerous effects in prolonged intake of vitamin A in amounts greater than 50,000 I. U.

Summary

Eight cases of chronic hypervitaminosis A have been observed in adults. The clinical features and pathogenesis of the intoxication are discussed together with the case of an 18-year-old woman who experienced pronounced hair-fall after an intake of 300,000 I. U. vitamin A daily for one year.

Zusammenfassung

Es wurden bisher 8 Fälle von chronischer A-Hypervitaminose bei Erwachsenen beobachtet. Es werden die klinischen Zeichen und die Pathogenese der Intoxikation diskutiert und auf den Fall einer 18jährigen Frau hingewiesen, die Haarausfall bekam, nachdem sie täglich während eines Jahres 300000 E Vitamin A eingenommen hatte.

Résumé

On a observé jusqu'ici 8 cas d'hypervitaminose A chronique chez des adultes. L'auteur discute les caractères cliniques et la pathogénèse de cette intoxication, ainsi que le cas d'une jeune femme de 18 ans qui avait présenté une importante chute des cheveux à la suite de l'absorption quotidienne de 300000 U.I. de vitamine A pendant une année.

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Erythema gyratum repens

By E. van DIJK

Cutaneous disturbances have been observed frequently in cases of internal malignant tumours and lymphoblastomas. They may be divided into specific and non-specific ("toxic") lesions. Many different non-specific skin eruptions have been described. Knowledge of these skin manifestations is of importance as they may be the first signs of internal disease (dermatoses monitrices des cancers, *Cougerot*).

In 1952, *Gammel* reported on a case of an unusual type of scaly erythema, named by him "erythema gyratum repens", associated with cancer of the breast. This case was originally presented by him as "erythema gyratum migrans".

The patient was a 55-year-old woman, who had undergone hysterectomy and oophorectomy 10 years previously. On the anterior surface of the neck and upper part of the chest a pruritic area appeared which gradually spread until it involved nearly the entire skin surface. On examination, the face and neck of the patient were found reddened and scaly with oedema of the eyelids and swollen vars, exudating in places. The entire trunk and the extremities showed irregular erythematous bands, not or only slightly infiltrated, with collerette-type, or marginal desquamation. The peculiar serpinginous configuration of the erythema resembled somewhat the graining of a knotty cypress board. The erythema moved constantly at the rate of about 1 cm. per day.

Histologic examination of the skin showed a slightly thickened stratum corneum, moderate acanthosis in the upper cutis, especially in the papillary layer, there was a perivascular infiltration of lymphocytes and small mononuclear cells. The connective tissue was oedematous.

A large lymph node in the left axilla was excised, and showed carcinoma. In the left breast a small nodule was palpable. After radical mastectomy (pathological diagnosis: poorly differentiated adenocarcinoma mammae) there was rapid improvement, and six weeks after the operation the eruption had disappeared completely.

Gammel reviewed the literature on rare and persistent erythemas. As the clinical picture of the erythema of his patient did not resemble the descriptions in the literature, he felt justified in classifying it as a new entity. He stressed its difference from erythema annulare

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Focal Retardation and Arrestment of Growth of Bones Due to Vitamin A Intoxication

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Retardation of growth and early closure of the epiphyses were observed in seven children hospitalized for severe symptoms of hypervitaminosis A. The acute symptoms abated after the excessive intake of vitamin A was stopped, but the bony changes were more lasting and in three cases the growth of the legs was seriously impaired. The large doses of vitamin A preparations had been administered to the children at home by their mothers, who had increased the dosages prescribed by their respective physicians. The evidence indicated that children differ as to the rate at which they metabolize vitamin A, and the amount of vitamin required to cause intoxication varied considerably.

THE FIRST REPORT of the toxicity of vitamin A in rats and mice was made by Takahashi and his associates [1] in 1925. The gross clinical findings in these laboratory animals included alopecia of the head and paralysis of the hind legs. Since then an exceptionally large number of publications have been concerned with the experimental and clinical manifestations of the effects of hypervitaminosis A on animals and humans. The earliest studies on bones affected by large doses of vitamin A were made in 1933 by Collazo and Sanchez-Rodriquez,[2] who, finding increased fragility of the bones in rats, designated the primary pathology as fibrous osteodystrophy. A year later, Davies and Moore [3] described ankylosis in the joints of the extremities of rats that were suffering from hypervitaminosis A. Experiments by Moore and Wang,[4] in 1935, indicated that altered metabolism produced by excessive vitamin A affected normal bone growth and development on the basis of faulty formation or destruction of the matrix.

In 1947, Wolbach [5] reported the results of vitamin A intoxication in guinea pigs and in rats; he demonstrated rapid remodeling processes of long bones due to increased osteoclastic activity and definite destruction of the epiphyseal cartilaginous plate which resulted in its premature closure. He stated that there was a lag in matrix production which accounted for compression of the cartilage cells adjacent to the diaphysis.

Tissue culture studies of the effect of embryonic bones grown in a medium containing large amounts of vitamin A were published in 1952 by Fell and Mellanby.[6] Using embryonic limb bone rudiments of chicks and long bones of fetal mice, they demonstrated that the growth of the explanted bones was retarded or completely arrested in direct ratio to the length of time the bones remained in the medium. Microscopic sections revealed that the epiphyseal cartilage cells lost their normal metachromosis and were crowded together because of shrinking of the intercellular tissue.

Experiments were conducted by Fell, Mellanby, and Pele,[7] who utilized embryonic bone rudiments which were subjected to carrier-free sulphur-35 as Na_2SO_4 and placed in an organic medium for culture. Autoradiographs were made, and from their studies the authors concluded:

> It is tentatively suggested that under the influence of vitamin A, the cartilage cells may produce an enzyme which results in the formation of a soluble sulphated mucopolysaccharide instead of the normal chondroitin sulphate, and in the dissolution of the existing matrix.

Recently, Thomas et al.[8,9] administered large amounts of vitamin A to rabbits; they confirmed Wolbach's findings of premature closure of the epiphyseal plates, but did not agree on the factors that produce the changes in the cartilaginous zones of the bones. They proved the presumption of Fell, Mellanby, and Pele that chondroitin sulphate was liberated from the cartilaginous matrix of the epiphyseal plate and demonstrated that this was followed by local vascularization and ossification of

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proliferating cartilaginous cells which ultimately resulted in arrestment of normal growth and altered tubulation of the long bones. Seventy-two hours after the rabbits were given excessive doses of vitamin A, examination of the sera by means of the cobalt precipitation method was interpreted as representing chondroitin sulphate.

Conclusive studies on the mode of action of vitamin A on cartilage in organ culture by Dingle, Lucy, and Fell [16] demonstrated the degradation of the extracellular material by enzymes released from lysosomal particles. Experiments by Dingle and Lucy[11] and by Dingle [12] disclosed that the water extract from embryo chicken limb organ culture contained a protease with an acid pH optimum and that the vitamin A altered the composition of the extracellular material, therefore advancing the hypothesis that the action of the vitamin is on the permeability of the intracellular particles. A report by Fell, Dingle, and Webb [13] demonstrated that their studies showed a high degree of molecular specificity for these effects. The work of Lucy and Dingle [14] on the lysis of erythrocytes by vitamin A has made it probable that the mode of action of the vitamin is on the lipoprotein membranes of cells and their organelles.

The first account of vitamin A intoxication in a child was offered in detail by Josephs [15] in 1944. The only reference made to bone changes in this article dealt with cortical hyperostosis that occurred in the long bones. Following Joseph's report, several additional cases of hypervitaminosis A in children that described similar findings were published. To the complications attributable to the administration of large doses of vitamin A in children can be added retardation and arrestment of growth of bones.

In this report, I shall concern myself with seven cases, three of which resulted in what may be considered serious alteration of skeletal development. The damage to cartilage cells is irreparable and full longitudinal bone growth is not attained. Not only is growth retarded, but occasionally serious premature closure of the epiphyseal cartilage takes place relatively early.

Vitamin A blood levels were made in only two patients; the remaining five cases were diagnosed on the basis of symptomatology, clinical examination, and roentgen study which demonstrated the typical cortical hyperostosis. When the diagnosis was established in five of the patients, vitamin A administration was discontinued and low vitamin A diets instituted. In one instance, a diagnosis of vitamin A intoxication was not made and concentrates were continued.

Roentgen Findings

In those patients in whom x-ray studies were made of the forearms and knees, cortical hyperostosis was found to involve the ulna and tibia and to reveal irregularity of the epiphyseal regions of the long bones associated with sharpening of their metaphyseal margins. During this phase of the roentgen studies there was no appreciable diminution in the altitude of the epiphyseal cartilage; later, there was definite thinning of the plate, which was most pronounced in the lower extremities because of the added insult of weight bearing. The distal portion of the metaphysis of the femur broadened abruptly and an outflare of its terminal portion gave it a pagoda appearance. A mirror-like image occurred in the adjacent tibial metaphysis. In addition to these changes, definite thinning of the cortex of the bone in the epiphyseal region occurred. There were instances of broadening of the shafts of the long bones and alteration of tubulation.

All the epiphyseal plates are involved in vitamin A intoxication and greater damage is done to one or more of the plates; this is explained on the basis of a greater amount of weight bearing on the respective extremity rather than on the other; or conversely, the favoring of the extremity which is more painful.

In the most severe cases, the epiphyseal cartilaginous plates became markedly narrowed, and ossification took place prematurely. Deformities and altered tubulation in the long bones also occurred. Vitamin A intoxication produces altered patterns of growth in all the long bones, and doubtless the epiphyseal plates of the vertebrae are likewise affected, interfering with normal development of the segments.

Reports of Cases

Case 1.—A seven-year-old white female child was admitted to the orthopedic service of The Children's Memorial Hospital on July 6, 1951, for treatment of a leg length discrepancy. Her history showed that she was born full-term; it was a breech delivery, she weighed 3 lb 15 oz; and her under-normal weight required that she remain in the hospital for one month. She walked when 17 months old. About this time the mother noticed that the child caused excoriations by excessive scratching. A physician prescribed a salve and every effort was made to avoid the contact of wool on the skin. This regimen afforded no relief over a period of two years, despite the efforts of several dermatologists, allergists and pediatricians who changed or eliminated soaps, prescribed ointments, instituted elimination diets, and administered diphenhydramine hydrochloride (Benadryl). To prevent scratching, the child wore slacks and long-sleeved blouses during the day, while mittens were worn at night. Since the child's red blood cell count was found to be 3 million, she was given a tonic for anemia.

X-ray films of the lower extremities taken on March 24, 1947, at the Samuel Merrit Hospital, Oakland, Calif., revealed only some possible slight irregularity in the zone of the epiphyseal plates of the lower end of the femur. A film on March 26 showed hyperostosis of the ulna. On March 27 at the same hospital x-ray films were said to show an inflammatory condition around bones of the arms and legs. The vitamin C intake was then increased. On April 4, a localized area of swelling on the left temporal region was noticed for the first time. One week later, the child had difficulty in walking. X-ray therapy was used to control the itching of the right arm and the right leg. The dosage given was 238 r.

On May 14, 1947, the child, then three years of age, was hardly able to walk and was admitted to the Stanford University Hospital. The report of the attending physicians[16] described a three-year-old child who was irritable, complained of pain in the arms and legs, and had generalized itching all over the body. The skin was found to be dry, and there was erythema of the left arm and left leg. Excoriations were present on the trunk and extremities, with loss of hair from the scalp, eyebrows and eyelashes. A firm, immovable mass measuring 2 cm by 2 cm was felt on the left side of the forehead; photophobia and strabismus were detected; and the left forearm was swollen and tender. The patient refused to walk because of pain in the left leg. The liver was enlarged, and was palpable two fingerbreadths below the costal margin. The serum calcium was 10.2 mg%, phosphorus 5.0 mg%, protein 6.9 gm%, and phosphatase 17 units. On the basis of the roentgenograms, a tentative diagnosis of leukemia, syphilis, or scurvy was made.

A report of vitamin A intoxication by Toomey and Morissette[17] published at this time described a similar symptomatology and this prompted the attending physicians to investigate the dietary history of their patient. They learned that the mother had been administering three scant, teaspoonfuls of vitamins A and D (Navitol) to her child instead of the three drops which had been advised originally. At a later date, the mother had administered 10 drops of vitamins E and C (Vipenta). The child consumed one-quarter of a teaspoonful of butter at breakfast and at lunch, and nearly a teaspoonful at the evening meal. The mother said that the child ate the butter that was unconsumed by the other members of the family. She drank a glass of milk at each meal, and an egg was included in her daily diet. The child's vitamin A blood level, taken May 22, 1948, was 913 units (normal 30 to 60 IU). Vitamin A was eliminated from her eating schedule and the child was discharged from the hospital improved. The vitamin blood level on Aug. 4, 1948, was 340 units. Roentgenograms made at that time were reported to be normal.

Apparently a misunderstanding took place, for the attending physicians reported that cod-liver oil was given the patient before admission to the hospital and that administration of vitamin A was resumed after her discharge in amounts sufficient to cause vitamin A intoxication on two occasions. In this connection, the mother emphatically stated that all food that contained vitamin A and proprietary preparations of vitamin A were discontinued and that no cod-liver oil was given.

At the time of her admission to the Children's Memorial Hospital, in 1951, the patient's right leg measured 55.5 cm and the left leg 50.5 cm. In an attempt to stimulate the growth of the shorter leg, ivory implants were placed in the medullary canal of the lower end of the femur and the upper end of the tibia. A second bone stimulation operation was performed on May 27, 1952, at which time metal screws were inserted in the upper end of the left tibia and a supracondylar osteotomy of the left femur was performed to correct a 20-degree flexion deformity at the knee joint. A section of bone from the head of the left fibula, including the epiphyseal plate, was removed for microscopic study. These sections revealed mature bone adjacent to the orderly growth of bone and the appearance of the cartilage cells of the epiphyseal plate.

The patient now is 18 years old. Her left leg is 5.0 cm shorter than the right and the difference is compensated by an elevation of the sole and heel of the left shoe. She is short in stature—height 4 ft 10½ in. Her father is 5 ft 11 in tall and her mother, 5 ft 4 in tall (Fig 1, 2, 3, and 4).

Case 2.—A seven-year-old female child, was referred to me by two physicians who have given permission to include their case in my series. The patient was first seen by one of these physicians in October, 1951, when she was 18 months old, because of shaking of the legs and tenderness of the

Fig. 1.—Female, age 3 years. Hyperostosis of ulna.

arms, associated with pronounced irritability. A tentative diagnosis of scurvy had been made by another physician. During the period of original complaint, the child developed a bilateral otitis media which was controlled by penicillin.

Examination revealed that the child held her head and back stiffly, although she was able to move her legs satisfactorily. She walked with an unsteady gait on the right side. Her extremities were painful on palpation. X-ray examination of the extremities revealed normal findings.

The physician's report said: "Subsequently after considerable consultation it was found that this child had been on excessively high doses of concentrated vitamin A and D and upon withdrawal of the vitamin preparation her symptoms disappeared and she appeared perfectly normal. Her subsequent history was uneventful until I saw her again in May, 1955. At that time she was brought to the office because her parents had noticed that the left leg was shorter than the right. The child had no complaint. The examination at that

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Fig. 2.—Sharpening of metaphyseal margins and slight bowing of tibiae of patient shown in Fig 3 and 4.

time revealed approximately 1 in. shortening of the left lower extremity which appeared to be confined to the femoral segment. The ranges of motion of the knee appeared to be essentially normal except for a very slight flexion of the knee joint. The x-ray examination revealed marked deformity of the distal femoral epiphysis with what would appear to be almost complete closure."

I saw this child on April 5, 1937; at this time the mother gave a history of administering one teaspoonful of oleum percomorph when the infant was one year old. At 18 months symptoms appeared and the infant was brought to the James Whitcomb Riley Hospital in Indianapolis. After 10 days, the child had so improved that she was discharged, even though a definite diagnosis had not been made. At home the mother increased the dosage of oleum percomorph to two teaspoonsful daily, and within three weeks the child became worse. Another physician was consulted, and, upon inquiring about the vitamin intake, he made a diagnosis of vitamin A intoxication.

At the time of my examination the patient's left leg measured 49.4 cm and the right leg 55.0 cm. There was a 5-degree flexion deformity at the left hip joint and a 15-degree flexion deformity at the left knee joint. The child wore an elevation on the left shoe. X-rays revealed gross thickening of the left femur, narrowing of the epiphyseal line, and flaring of the adjacent margins of the metaphysis.

Case 3.—A five-year-old female was seen by me on Sept. 1, 1937, because of a leg-length discrepancy which had not been noticed until three or four months previously. The child was full term and walked at the age of one year. When she was three and one-half months old she was treated at the Columbus Hospital, Chicago, for virus pneumonia. At the age of 15 months she refused to stand or walk because of extreme pain and tenderness of the extremities the child was carried on a pillow. She was admitted to the Presbyterian Hospital, Chicago, at which time a roentgen diagnosis of scurvy was made and ascorbic acid was prescribed. When I saw her on Sept. 5, 1938, the child walked with a limp on the right side. There was obvious shortening of the right leg, its length was 46.5 cm compared with 49.6 cm of the left. Motion at all the joints of the extremities was complete except that there was a 10-degree limitation of motion of the right thigh that prevented complete extension at the hip joint.

X-ray films of the femora disclosed the typical pagoda appearance at the left lower metaphysis that is found in vitamin A intoxication. There was also shortening of the femoral neck. Presbyterian Hospital kindly furnished the x-ray films made on April 5, 1935, which demonstrated hyperostosis of the ulna and irregularity of the ends of the radius and ulna, not unlike scurvy. The metaphyseal margins appeared to be sharpened.

It was learned from the mother that the infant was given a 0.6 cc of a multiple vitamin preparation (Polyvisal) when three weeks old. At the same time she was receiving the yolk of one egg daily and all of the vegetables were generously buttered. A bone stimulation operation was performed on the left femur and tibia at The Children's Memorial Hospital on Nov. 4, 1938, with the hope that advantage could be taken of what remained of the cartilage cells of the epiphysis. When last examined on May 7, 1962, the right leg measured 58.2 cm, and the left 65.0 cm.

Case 4.—A 22-month-old female was admitted to The Children's Memorial Hospital on July 28, 1932. The mother stated that at the age of nine months the child began to walk. At 15 months she became unsteady on her feet and refused to walk because of pain in the legs. The pain and tenderness of the extremities gradually became worse, to such an extent that the child cried out whenever she moved.

Examination revealed marked tenderness of the extremities, but was otherwise negative. The admitting diagnosis was scurvy. Blood studies revealed the ascorbic acid level was 0.9 mg%, calcium 10.4 mg, phosphorus 3.3 mg, and alkaline phosphatase 5.7 units. No vitamin A determination was made.

X-ray films of the left forearm showed the hyperostosis of the ulna typical of vitamin A intoxication. There were also irregularities of the metaphyseal ends of the radius and ulna. The films of the lower extremities revealed sharpening of the femurs at the juxta-epiphyseal zones.

After the diagnosis was established by x-ray, all vitamins were discontinued and the child was placed on a vitamin A-free diet. She was discharged from the hospital on July 30, 1932. After five days at home the child began to walk and all the pain in the extremities had disappeared. Approximately six months later roentgenograms of the lower extremities revealed residual irregularity at the epiphyseal zone. X-ray films of the femurs made on March 7, 1937, showed definite broadening of the right femoral neck and enlargement of the capital epiphysis. The bones of the lower extremities appeared to be normal. She was last examined on June 9, 1962, at which time she appeared to be in good health. The length of the right leg was 79.2 cm and the left was 76.6 cm.

Case 5.—A 13-month-old female was admitted to our hospital on June 19, 1918, with the history that two and one-half months previously she had had pain and tenderness in both legs, which lasted only a few days. However, at the time of admission she was not able to stand or to walk and had not been able to do so for two days. She cried out when she was touched, because her legs were extremely tender. Examination was essentially negative except that the legs were sensitive and were covered with excoriations.

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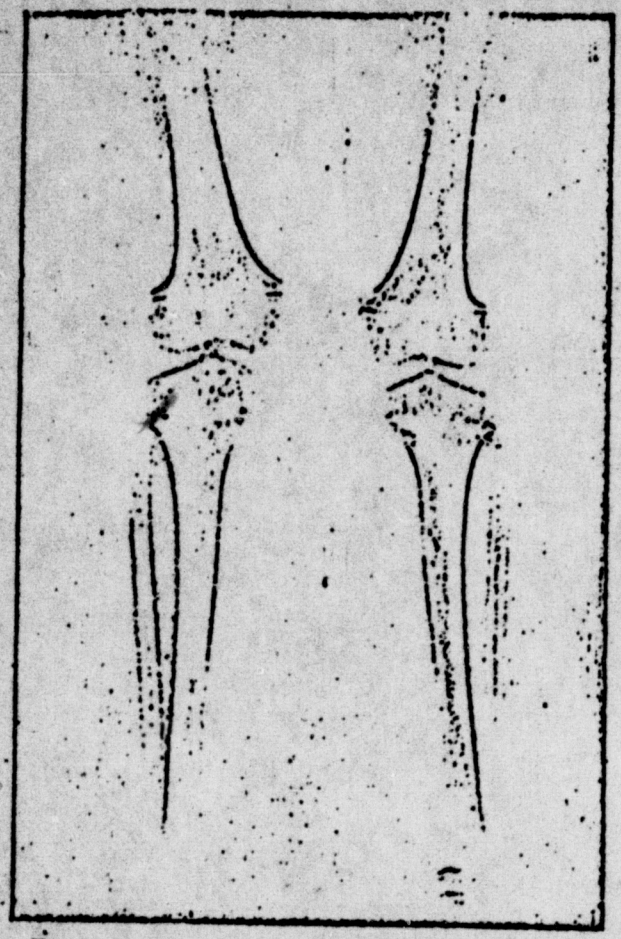

Fig. 3.—Same patient 2 years later. Pagoda-type spreading of metaphyses. Thinning of epiphyseal zones plates of lower femora and tibiae. Alteration of tubulation of femora and tibiae with moderate in-bowing of latter. Obvious shortening of left tibia.

Fig. 4.—Four years later. Both lower femoral and upper and lower epiphyseal plates of left tibia show marked degeneration and alteration of normal pattern of bone growth. Distal cartilaginous plate of right tibia is narrowed, but contour of bone appears to be normal.

Rectal temperature was 100.5 F (38 C). The impression was that this child had cortical hyperostosis of undetermined origin, possibly scurvy or congenital syphilis. Routine blood and urine studies were negative. Neither the vitamin A nor the vitamin C level was determined.

Roentgen studies revealed extensive hyperostosis of ulnae, femora, and tibiae. There was irregular growth at the juxta-epiphyseal regions and in-bowing of the tibiae. Since the roentgen findings were typical of hypervitaminosis A, inquiry disclosed that this child had been given indeterminable amounts of vitamin A concentrates. After vitamin A preparations were eliminated and a diet low in vitamin A values was instituted, all the symptomatology disappeared.

When the patient was examined on April 29, 1951, there was minimal shortening of the right leg compared with the left, the measurements being 87.3 cm and 88.0 cm, respectively. X-ray examination revealed that the extremities were normal, but there was alteration in growth of the vertebrae in the lower dorsal region, especially the 10th and 11th segments.

Case 6.—A 15-months-old female was admitted to our hospital on June 4, 1950, with a history of poor appetite, irritability, swelling in the temporal region, and tenderness of the legs. The mother stated that the child received 10 drops of oleum percomorph at the age of one month and she gradually increased it to one teaspoonful daily. When the child was nine months of age a multiple vitamin preparation in amounts of 10 drops were given three times a day in addition to the daily teaspoonful of oleum percomorph. Vitamin A blood level shortly after admission was 250 units.

X-ray films of the child's forearm revealed typical hyperostosis of the ulna associated with some irregularity of the metaphyseal margins of the radius and ulna. Upon withdrawal of the vitamin A and after the child was placed on a vitamin A-free diet, she made a complete recovery. She was discharged from the hospital on June 15, 1950. Examination on July 14, 1950, revealed that the left leg was 0.3 cm shorter than the right. On May 6, 1951, the left leg still was 1.0 cm shorter than the right. The degree of damage to all of the epiphyseal plates is speculative, but no doubt there has been more destruction of the cartilaginous plates of the bones of the right lower extremity than there has been of the left.

Case 7.—A 22½-month-old male was brought to the private outpatient department of our hospital due to a one-week history of inability to walk and pain and tenderness in the legs. The mother stated that the child's hair began to fall out a month previously. Because of extreme tenderness of the extremities, examination was almost impossible. On inquiry, the mother stated that she had given the child a dropper full of oleum percomorph daily since infancy, but did not know the exact amount. When the child was 13 months old, the dose of the concentrate was doubled. Vitamin A intoxication was suspected. For expediency, x-ray films were made of the left forearm, which demonstrated

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hyperostosis of the ulna and irregularity of the radius and ulna at the level of the epiphyseal plates, typical of vitamin A poisoning.

This child was not admitted to the hospital, but all vitamin concentrates were discontinued and a vitamin A-free diet was prescribed. Within a week all the symptomatology that had been present earlier disappeared. This boy was last examined on Aug. 30, 1961, at which time the right leg measured 78.7 cm and the left 80.3 cm.

Comment

The statement that 200,000 units of vitamin A may be given to a child each day with impunity appears to be erroneous. It is my opinion that the metabolism of vitamin A is not a constant factor for all children. The degree and rate of absorption of vitamin A varies with the individual child. These facts are borne out by the experiments of Thomas and his associates [8] who found that one of seven rabbits that received 1,000,000 units of vitamin A for five days showed no cobalt-precipitable material (chondroitin sulphate), whereas of 23 hypervitaminosis A rabbits, 8 showed no changes in the cartilage.

This study raises the question of what effect carotenoids have on the growth of bones in children. More than 40 years ago Steenbock [18] and his associates recognized the close relationship of carotene and vitamin A. B. and H. Von Euler, and Karrer [19] proved that carotene was biologically similar to vitamin A in its effect and indicated that there was a close relationship between the two compounds. Karrer, Morf, and Schopp [20] demonstrated that the uptake of water by one β-carotene molecule converts the latter into two molecules of vitamin A. The findings that I have presented in the retardation of growth of bones in children because of avitaminosis A may explain the short stature of people in certain parts of the world where there is a large intake of provitamin A carotenoids, frequently designated as yellow pigmented fruits, vegetables, and flowers. Karrer and Jucker [21] list ten natural carotenoids they consider to be in the class of provitamin A. Moore [22] devotes a chapter on transfer of vitamin A to the offspring.

Conclusion

Vitamin A in excessive amounts may inhibit growth of bones in children and cause premature closure of the epiphyses. Seven cases are presented with data which add a new complication from overdoses of this vitamin.

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Chronic Hypervitaminosis A

Report of a Case in an Adult

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AND

JOHN L. SOSCIA, MD

NEW YORK

adult case

Arch. Int. Med. 112: 462-66, 1963

Introduction

Hypervitaminosis A has been described in seven adults since Josephs' first report of a case in a young child in 1944.[1] Since then 36 well-documented cases in infants and young children have been reported.[2] Knudson and Rothman [3] divide hypervitaminosis A into acute and chronic forms as they exist in infants and adults. The acute is self-limited and occurs subsequent to the ingestion of a large single dose of vitamin A. Rodahl and Moore [4] in 1942 described the toxic symptoms of acute hypervitaminosis A in Arctic explorers; this hypervitaminosis A resulted from ingestion of polar bear liver. The chronic form may exist for years without recognition. All adult cases thus far described in the medical literature are of the chronic type.[5]

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The present-day sales of vitamins emphasize the awareness that must be exerted by physicians in the consideration of this clinical entity. Drugstore sales of vitamin products reached a total of 250 million dollars in 1960.[6]

Report of Case

A 39-year-old white unmarried female secretary presented herself to the Emergency Room at The St. Vincent's Hospital of the City of New York on Dec 19, 1962, because she had sustained trauma to her left big toe. Edema of her legs was noted, admission to the hospital recommended, and the following history was elicited from her.

Since February, 1962, she had noted mild swelling of both feet, ankles, and legs. Initially this was intermittent in character but became constant and more marked during the four weeks prior to admission. During the previous year she had also noted weight loss, lassitude, excessive fatigue at work, and severe intermittent pains in her shoulders, wrists, and knees. Four weeks prior to her admission to the hospital, walking had become very difficult because of pain "deep inside" her legs. For six months she noted that her hair was falling out. At the same time, a pruritic rash on her arms and reddish discoloration of her ankles and feet appeared. She complained of frequent mild frontal

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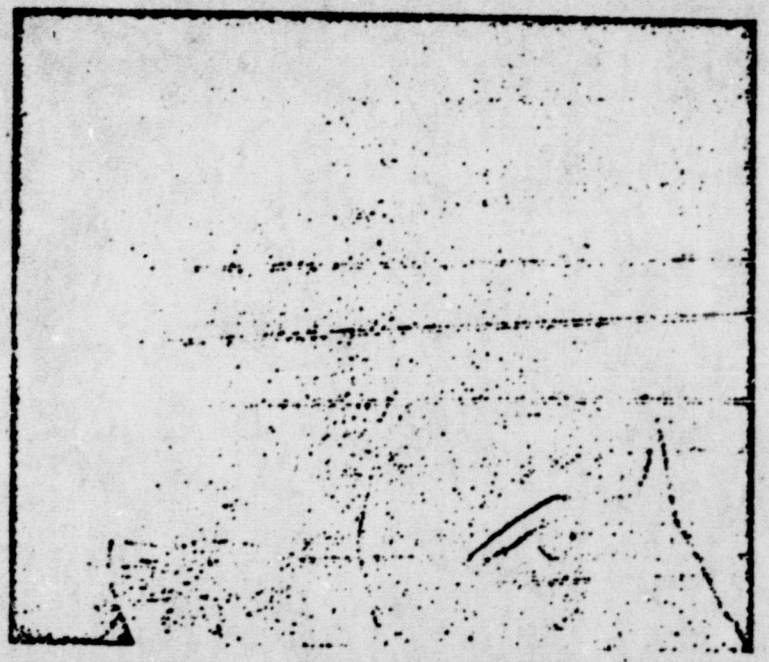

Fig 1.—Sparse coarse hair over frontotemporal region and thinning of the eyebrows and eyelashes.

headaches. In spite of these symptoms she did not seek medical help.

She denied dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, chest pain, or palpitations. There was no history of cardiac, hepatic, or renal disease, and she had not experienced constipation or menstrual irregularities. The patient had never been hospitalized before.

Eight years ago she started taking multivitamin preparations and individual tablets of vitamin A to improve her vision. She took three to six tablets of 25,000 units each of vitamin A daily up to July, 1962, at which time she increased the intake to five tablets per meal because of tiredness during the summer months. She continued taking this dose of vitamin A until admission to the hospital.

Physical examination revealed a well-developed, thin, tired-looking 39-year-old white woman. She was well oriented and cooperative. Vital signs were within normal limits. Examination of the head showed sparse coarse hair over the temporal and occipital regions (Fig 1). Marked thinning of the eyebrows and eyelashes was apparent. The eyes were not prominent, and there was no lid lag. Funduscopic examination was negative. An acneiform rash was present over both malar eminences. The thyroid gland was not palpable. The lungs were clear to percussion and auscultation. The heart was normal. The abdomen was soft, and a firm, smooth, nontender liver was readily palpable 5 cm below the right costal margin in the midclavicular line. The tip of the spleen was also felt. Pelvic and rectal examinations were within normal limits. Moderate edema below the knees down to and including the dorsum of the feet was present in both lower extremities. A confluent erythematous rash with prominent petechial hemorrhages was apparent on the lower third of her legs, ankles, and down to the midportion of the dorsum of her feet where it was demarcated abruptly by her shoes (Fig 2). There were no varicose veins. A fine macular rash was present on the inner aspect of both upper extremities. Here the skin showed prominent follicles and was very dry. Examination of the rest of the body revealed sparse pubic and axillary hair. There was no lymph node enlargement. Moderate pressure over both knees, tibias, and ankles elicited severe pain, as did pressure over her shoulders and humeri, but to a lesser degree. The patient complained of severe pain in both feet, legs, and knees when standing up. Neurological examination revealed no abnormal gait or tremors. Deep tendon reflexes were normoactive and symmetrical. There was no sensory deficit. Motor power and coordination were within normal limits.

Laboratory data on admission revealed a hemoglobin of 10.2 gm and normal white blood cell count, differential, and platelet count. Peripheral blood smear showed normocytic and normochromic red cells. Urinalysis, serological test for syphilis, fasting blood sugar, and blood urea nitrogen were all within normal limits. Serum electrolytes, including calcium and phosphate levels, and three lupus erythematosus preparations were normal. A latex fixation test was negative. Urine examination for Bence Jones protein gave a negative reaction. Twenty-four-hour urine calcium excretion was 7.5 mEq. Total serum cholesterol was 161 mg per 100 ml. Prothrombin time was 17 seconds with a control of 13 seconds. Stools showed no occult

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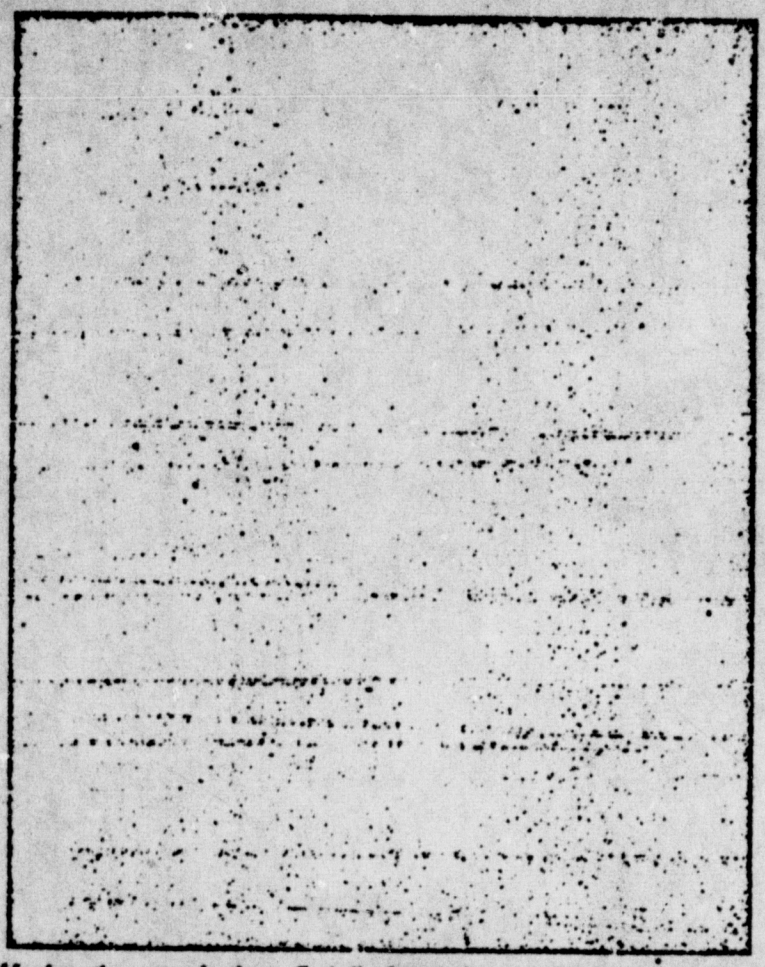

Fig 2.—Confluent erythematous rash with prominent petechial hemorrhages demarcated abruptly by shoes on dorsum of feet. Moderate edema of ankles and lower legs.

blood on three examinations. Cephalin flocculation, thymol turbidity, serum glutamic oxaloacetic and pyruvic transaminases, and lactic dehydrogenase were all normal. The total serum bilirubin was 1.7 mg per 100 ml with a direct fraction of 1.5 mg. Alkaline phosphate was 12 Bodansky units, total serum protein 5.7 gm per 100 ml with an albumin of 2.8 and globulin of 2.9 gm per 100 ml. Electrophoretic pattern of serum proteins showed no abnormalities. Sulfobromophthalien retention 45 minutes after intravenous injection of 225 mg of the dye was 17%. Serum iron was 98μg per 100 ml and serum iron-binding capacity 366μg per 100 ml. Twenty-four-hour I^{131} uptake was 18.6%. Serum protein-bound iodine was 3.3μg per 100 ml, and the basal metabolic rate was —2.

An admission electrocardiogram and chest x-ray were normal. Skeletal survey showed no bony abnormalities. Upper gastrointestinal and large bowel x-ray studies were within normal limits. Bone marrow examination was normal.

A liver biopsy performed on the 28th day and stained with hematoxylin and eosin was also normal.

Fasting serum vitamin A level on the eighth hospital day was 874μg per 100 ml (normal 30μg-70μg), and a serum carotene level at the same time was 182μg per 100 ml (normal 100μg-200μg).

Hospital Course.—The patient was placed on a regular hospital diet (5,000 units of vitamin A per day), and all medications were withdrawn. By the third hospital day the edema of her legs had disappeared, without weight loss. She continued to complain of frontal headaches almost daily during the first week of hospitalization, but these gradually disappeared over the ensuing two weeks.

By the end of the first week in the hospital the pain in her lower extremities had diminished although her legs and knees were still tender when moderate pressure was applied. After the second week she was walking without leg pains. The rash on her arms, face, and lower extremities was less apparent. She did not complain of pruritus and felt less tired. At the end of the fourth hospital week her liver was still palpable but had receded 2 cm, and the tip of the spleen could be felt with difficulty. She had normal bowel movements and a normal menstrual period while in the hospital. A second

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fasting serum vitamin A determination five weeks after admission was 769μg per 100 ml. Ascorbic acid level the same day was 0.7 mg per 100 ml (normal 1 to 2 mg per 100 ml).

The patient was discharged on the 36th hospital day complaining of minimal pain in the legs when walking. There was no change in her alopecia at the time. Instructions regarding avoiding foods with high vitamin A content were given to her. She was seen in follow-up clinic two weeks later, and at that time a fasting serum vitamin A level was 527μg per 100 ml.

Comment

Hypervitaminosis A appears to be a well-recognized syndrome in children and adults. Different individual responses to elevated doses of vitamin A exist. The onset of the condition is insidious and follows a variable latent period of weeks to 8-10 months.[7]

Vitamin A intoxication may be confused with many pathological states since it involves many systems. In one of the reported cases [8] the differential diagnosis included brain tumor, serous meningitis, chronic encephalitis, viral radiculoencephalitis, psychoneurosis, and infectious arthritis. To this list may be added Addison's disease (adrenal cortical hypofunction), hypothyroidism, hepatitis, and the collagen disorders.

The reticuloendothelial system is commonly involved in vitamin A intoxication. Hepatosplenomegaly and lymph node enlargement have been reported in five adult patients.[5,8-11] Liver enlargement is considered to be due to large deposits of vitamin A in the liver since vitamin A is chiefly stored in this organ.[12] Bifulco, however, feels that hepatosplenomegaly may be explained by deposition of fat in these organs.[13]

Using fluorescence microscopy, vitamin A can be visualized in tissues. A striking green fluorescence is imparted by this substance to the lipoids which carry it, the degree of fluorescence depending on the amount of vitamin A present.[14] Liver biopsy specimens from other reported cases of hypervitaminosis A are not available. In the present case, routine histological methods did not show any abnormality.

Hypoprothrombinemia, hypoproteinemia, and elevated serum alkaline phosphatase without evidence of bone disease may be explained in this patient on the basis of hepatic dysfunction. Anemia was noted in one other adult patient with hypervitaminosis A.[13] The exact mechanism of its occurrence is not known. Stimson [5] feels it is probably related to the hypervitaminosis, since it is a common finding in animals. Josephs [1] indicates that normal bone marrow may be replaced by pathologic tissue to account for the hypoplastic anemia that occurred in his case. The hemorrhagic dermatoses (Fig 2) of both lower extremities as noted in this case may be related to increased capillary fragility secondary to hypovitaminosis C. Animals with experimental hypervitaminosis A show low serum ascorbic acid levels and decreased amounts of ascorbic acid in the adrenals and liver.[15]

Neurologic manifestations in this disorder are directly related to increased intracranial pressure, perhaps secondary to excess production of spinal fluid.[8] Unrelapsing, progressively severe headache was a constant complaint of our patient.

Arthralgias with bone tenderness have been noted in all of the previously described adult patients.[5,8-11,13,16] In children bone pain is due to periosteal thickening, and premature closure of the epiphyses with growth retardation may occur.[17] Radiographic bone changes have only been demonstrated in one adult case.[8] Increased urinary excretion of calcium with normal serum calcium and phosphorus has been described.[13] The low-normal protein-bound iodine, radioactive iodine uptake, and basal metabolic rate in the present case may be explained by the direct counteractive effect of vitamin A on thyrotropic hormone and thyroxin.[18,19]

Dermatologic changes are a common occurrence after excessive intake of vitamin A. Loss of body hair with thinning of eyebrows and lashes, pruritus, and dry skin are described in the case report. The skin manifestations resemble those of vitamin A deficiency.

As noted by Stimson,[5] nonspecific symptoms were present in all patients. Unremitting fatigue was the most significant and disabling.

Treatment consists of withdrawal of vitamin A. Subjective symptoms usually disappear within two weeks, but hepatosplenomegaly and alopecia may persist for months.[8,10] Elevated serum vitamin A levels may persist for months following withdrawal and may in some cases be related to the size of the dose and duration of vitamin A intake.[8] The fasting serum vitamin A level of 874 μg per 100 ml reported in this patient is the highest ever recorded in a case of chronic intoxication with this substance.

Summary

A case of chronic hypervitaminosis A in a 39-year-old white female is described. The main signs and symptoms included fatigue, weight loss, bone and joint pains, bone tenderness, loss of body hair, pruritus, dry skin, hepatosplenomegaly, anemia, headache, and skin rashes. Similarities and differences between this case and the others reported are mentioned.

Treatment is specific and curative, consisting in withdrawal of vitamin A.

Arthur L. Levy, PhD, performed the vitamin A determinations.

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Ballistocardiographic Patterns and Nicotine

Types of Ballistocardiographic Patterns Evoked by Nicotine and the Relation of the Most Frequent Pattern to Effects of Nicotine on Respiration, Not on the Heart

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Many reports of changes evoked by nicotine in the high-frequency head-foot ballistocardiogram have appeared in the last decade.[1-14] These changes often occur in people known to have heart disease or Buerger's disease (thromboangiitis obliterans), but they have been observed in 5% to 15% of normal subjects. There has been no study of the mechanisms underlying positive tests, but it has been assumed that coronary disease might be a factor in predisposing to the change in pattern evoked by smoking or chewing tobacco or by the administration of nicotine. The possibility that some of the changes might be due to noncardiac factors was suggested by studies of the respiratory variation in systolic ballistocardiographic waves in records made with Starr's method or by devices recording motion of the body in relation to the surface on which it rests.[15,16] The findings of a study of positive smoking tests on normal subjects are presented here.

Methods

The motion of a platform (50×44 cm) mounted on stiff springs was recorded as described previously.[17] This platform was placed under the pelvis and thighs of the subjects, while respiratory motion of the sternum was recorded by a photocell and light beam and that of the abdomen by a Harvard pneumograph and strain gauge. The first derivative of the brachial pulse was recorded with a glycerin capsule and piezoelectric sensing device. The respiratory records were made with direct-current amplifiers, and the baseline was constant in these experiments.

The subjects were 14 men, aged 21 to 28, and 5 men, aged 45 to 55. All were in good health, with normal blood pressure and no evidence of latent heart disease. They were selected because they were habitual smokers, smoking 20 to 30 cigarettes daily. Two of the older subjects preferred to smoke six or more cigars daily. The younger men were known to have family histories of vascular disease, and eight were markedly overweight.

Results

In two of the younger group and one of the older men, smoking produced a change from normal to grade 2 abnormality in respiratory variation in systolic force. In six of the younger men, and one of the older men, grade 1 abnormality appeared on smoking. One young man went from grade 1 to grade 3 on smoking. One of the older men had grade 2 abnormality before smoking, and the pattern became slightly less abnormal during and after smoking. Only the 11 men with positive tests are considered in what follows, but it should be noted that some of the men with no increase in respiratory variation in systolic waves after smoking showed an increase in pulse rate and decrease in rate or depth of respiration,

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Medical Service, Kings County Hospital Center, and Department of Medicine, State University of New York Downstate Medical Center.

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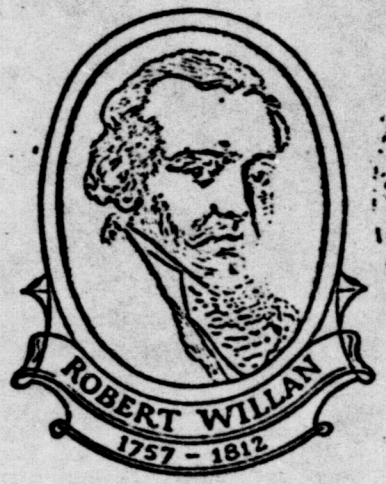

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EASTERN COUNTIES DERMATOLOGICAL SOCIETY.

Ipswich, 8 June 1963.

Juvenile Pityriasis Rubra Pilaris and Vitamin A Intoxication.—Dr. J. Lyon and Dr. J. W. Paulley.

A boy aged 12.

History.—Since birth, dry scaly red skin, aggravated by sunlight; no bullae. Is only one in family affected. First seen in 1956, aged 6. Diffuse redness and scaling including flexures. Seborrhoea of scalp with marked greasy scales. Scanty eyelashes and eyebrows. On dorsum of outer two fingers some follicular plugging. Palms and soles not yellow. Commenced vitamin A 150,000 units t.i.d. without benefit. 1957, dosage increased to 200,000 units q.i.d. with definite benefit. 1958, developed headache, tinnitus, vomiting, unsteady gait, and papilloedema associated with hydrocephalus. Craniotomy and posterior fossa exploration and decompression. A.E.G. normal. Ventriculography confirmed hydrocephalus.

October 1960, relapsed with lethargy, aching in legs since restarting vitamin A up to two weeks ago. Discs blurred, wasting and weakness of lower limbs. Later improved following physiotherapy and avoidance of vitamin A. December 59, restarted vitamin A, 200,000 units daily. No skin improvement. Gradually increased to 600,000 units daily over 1 year. July 61, vitamin A discontinued as he became dizzy and weakness with aching in legs returned. There was some wasting of the interossei muscles of the hand, while the optic discs showed no papilloedema. His jerks and sensation were normal. He felt better when off vitamin A. Since August 61, there has been some spontaneous improvement of the skin as he reached puberty.

Investigations.—Skull and chest x-rays normal 1959. Toxoplasmosis tests negative. Blood count normal. Histology (1961) showed minimal follicular hyperkeratosis.

Discussion.

Professor Cawley said he had had a similar case of vitamin A intoxication—this side effect of raised intracranial pressure was not generally well known.

Acrodermatitis Enteropathica.—Dr. J. Lyon and Dr. J. W. Paulley.

A boy aged 13.

History.—After 6 weeks of age, vesicular eruption on face, forehead, neck and buttocks, occurring in crops every few days, up to the age of 3 years, when they were replaced by desquamating psoriasiform lesions with fissuring round the orifices, nail deformity and complete alopecia. Diarrhoea was present intermittently and at times he became irritable, ill and photophobic, with secondary skin infection.

On examination.—April 1954, age 5 years, he was underweight, miserable, photophobic; there was complete alopecia, widespread extensive, red, desquamating lesions, including hands and feet, and nails were deformed. Corners of mouth were fissured, and buccal cavity showed ulceration; teeth normal. Apart from diarrhoea, no other abnormality detected in any other system.

Investigations.—Monilia recovered from the stools and mouth, but no pathogenic bacteria. Skin lesions showed *Staph. pyogenes* and monilia.

Treatment and progress.—Diodoquin 210 mg. daily, increased to 600 mg. q.i.d. Skin, hair and nail improvement began after a few weeks, but after 2 months sterile bullae reappeared and scaly dermatitis returned, but without diarrhoea. His health gradually improved after spending a long spell in hospital from March 1954 to December 1958. He was maintained in excellent health (though underweight for his age) on diodoquin 300 mg. q.i.d. His hair was growing well, teeth rather carious; nails, though improved, still dystrophic. Slightly backward at school. He had a dry scaly patch on his left ankle and some milia on neck.

March 1958: An attempt was made to reduce dosage to 300 mg. b.d. but a skin relapse occurred within one week consisting of scaling and crusting round upper lip, neck and left ankle, from which neither pathogenic bacteria nor monilia could be isolated.

January 1962: When the diodoquin was reduced to 325 mg. t.i.d. he began to relapse so he was re-admitted. He was lethargic, photophobic, pale and off his food. His scalp hair became very scanty. Blisters developed on left heel, becoming ulcerated. There were psoriasiform lesions on elbows, popliteal fossae, ankles, genitalia and corners of mouth. His nails remained dystrophic. Milia in scars on neck and in lumbar region.

Further investigations.—No hypoparathyroidism. Serum Ca 8·8 mg.%. P 4·3 mg.%. Numerous tests for malabsorption were normal. Serum proteins, carotene, iron, urea, Cl, K, Na, alkaline phosphatase, urinary FIGLU, xylose, 17-ketosteroids and screening test for amino-acids, faecal fat, glucose tolerance test and fractional test meal normal. Hb. 70%, P.C.V. 34%, M.C.H.C. 30, M.C.D. 6·9. W.B.C. 9,000 per cu. mm. E.S.R. 15 mm. Stools and sputum grew *Candida albicans* but skin scrapings did not.

Skin biopsy left knee: "Marked hyperkeratosis, with some acanthosis. The rete ridges are broad, deep and rather plexiform."

Jejunal intubation and biopsy carried out by Dr. Paulley. "The mucosa was abnormal with villi having branched whorls." Duodenal fluid culture was sterile. It was not assayed for enzymes.

Small bowel barium meal: some clumping of the barium.

Further treatment.—He responded to 650 mg. diodoquin q.i.d., a gluten free diet and long-term oxytetracycline therapy.

(Previously shown at Section of Dermatology, Royal Society of Medicine, in April 1954 and May 1959.)

Congenital Ichthyosiform Erythrodermia and Idiopathic Steatorrhoea.—Dr. J. Lyon and Dr. J. W. Paulley.

A woman aged 29.

History.—Since birth dry scaly skin all over. No one else in family affected. From time to time large blisters develop at various sites all over the body. March 1962, developed diarrhoea with fluid, non-bloody motions usually at night. Also some anorexia and weight loss.

P.H. Skin grafting attempted but failed, when aged 14.

Examination.—Congenital ichthyosiform erythrodermia (Brocq). Whole body involved with predilection for flexures. Face, calves and palms erythrodermic but relatively free of gross scaling. Some resemblance to famous Suffolk Porcupine family (Lamberts). Flaccid bullae seen at times on legs and abdomen, leaving denuded areas after rupture.

Investigations.—Blood count normal. Three day faecal fat output raised. Stool looked abnormally fatty. No pathogens found. Serum mucoproteins raised—200 mg.%. Carotene low, 76 μg. Jejunal biopsy abnormal. Sigmoidoscopy normal. Chest x-ray and barium meal normal. Small bowel meal, some clumping. Urine no porphyrins.

Skin biopsy. Predominent feature is enormous hyperkeratosis without parakeratosis. The malpighian layer is narrow and disorganized and stratum granulosum is irregular and disorganized. The dermis is normal. Appearance is that of ichthyosis congenita.

Treatment.—On gluten free diet, stools only once a day. Vitamin A 50,000 units t.i.d.

Thirty-five other cases were also shown and Dr. E. F. Edson of Fison's Research Centre read a paper on *Dermatological Aspects of Agricultural Chemicals*.

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including a section of the

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plaques of necrotic tissue clear in the tissue

deep in the tissues, in the marrow spaces of which a gram-positive, filamentous, branching organism could be demonstrated. There was also considerable resorption of the cementum and dentine of the adjacent root of a vital lower incisor which had been removed en bloc with the epulis.

It was not, of course, possible to type this filamentous organism from the appearances in a tissue section alone, but morphologically it was indistinguishable from actinomyces.

It is suggested that, where chronic granulomatous lesions occur in the mouth in association with resorption of adjacent teeth, the possibility of an actinomycotic infection should be considered.

The authors wish to express their gratitude to Dr. J. M. McWilliams of the Department of Bacteriology, University of Edinburgh, for her assistance in this case, and also to Mr. A. Hunter and Miss M. Forfar for technical assistance.

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ORAL MEDICINE

HYPERVITAMINOSIS A

Report of a Case

Joe H. Smith, D.D.S., Dallas, Texas

Hypervitaminosis is most commonly associated with the fat-soluble vitamins, especially vitamin D. Hypervitaminosis A has been reported rarely. However, the effects of overdosage of this essential vitamin for long periods of time are serious enough to make one aware that hypervitaminosis A may produce certain oral lesions. Also, the common practice of prescribing this vitamin for skin problems, especially among teenagers, adds to the necessity for considering the possibility of hypervitaminosis A in this age group when oral lesions are present.

The symptoms of hypervitaminosis A described by Goodman and Gilman[1] include subcutaneous swellings in the forearm, shanks, feet, and elsewhere. The lesions are tender and painful and cause hyperirritability and limitation of motion. Multiple bone lesions, which are usually present under the subcutaneous swellings, can be seen roentgenographically and can be demonstrated as hyperostoses. Other signs and symptoms which may be present include anorexia; pruritus; dry, scaly lips; bleeding fissures at the corners of the mouth; dry, excoriated skin; and sparse, coarse hair. Plasma vitamin A may reach a level from 400 to 2,000 units per 100 ml.

The syndrome of hypervitaminosis A reported in an adult by Sulzberger and Lazar[2] included joint and bone pain in addition to the above symptoms. That patient had a daily intake of 600,000 units or more.

In children, an intake ranging from 75,000 to 500,000 units daily has caused a hypervitaminosis A. Usually these high intakes have resulted from overzealous prophylactic vitamin therapy on the part of parents who have confused pereomorph-liver oil with the less potent cod-liver oil. There is a latent period of 6 months or more between the start of excessive dosage and the appearance of diagnostic clinical signs of poisoning.

The following case is thought to be fairly representative of hypervitaminosis A, except that no hyperostoses were demonstrable roentgenographically, as seen in the left forearm.

Fig. 2.

Fig. 4.

CASE REPORT

The patient, a 14-year-old white boy, was seen on June 1, 1961, with complaints of swollen, bleeding, and tender gingivae. The condition had been present for several weeks but had not been severe enough to send him to a dentist. His physician referred him for periodontal examination and consultation after observing the oral condition during his physical examination of the youth. The history revealed that the patient had been wounded in a hunting accident about 8 months previously. His right arm was shattered by a shotgun blast, but surgical intervention had prevented its loss. Shortly after leaving the hospital, the patient developed an acnelike condition on his face and went to a dermatologist. Along with other therapy, vitamin A in the amount of 50,000 units daily was prescribed.

At the time I first saw the patient he was taking 300 mg. of vitamin C, 300,000 units of vitamin A, and 1 grain of thyroid extract daily. His physician had prescribed the thyroid extract to help overcome the lethargic condition which had developed. The patient had decided that if 50,000 units of vitamin A was good, six times that amount would be that much better. His physician was not aware that he was taking this excessive amount of vitamin A. The vitamin C was being given empirically to help in the healing of the wounded arm. In addition to the marginal gingivitis (Fig. 1), the lips were dry and scaly (Fig. 2) and bled easily. Further questioning disclosed that the patient was bothered by itching, dry skin, painful shins, and loss of appetite. He admitted to taking excessive doses of vitamin A over a 6 month period.

The rest of the history was negative, except for the drinking of one quart of skim milk daily and a carbonated orange drink which the patient thought gave him an "energy boost." The dental examination revealed teeth that were crowded in the anterior region but free from caries. The functional relation of the arches was good. The patient brushed his teeth once daily after breakfast, and the teeth appeared clean and well cared for. The degree of gingivitis was out of all proportion to the local irritants present. Treatment consisted of eliminating the skim milk, orange drink, vitamin A, and thyroid extract. The patient was furnished with a disclosing solution (basic fuschin in alcohol) and given instructions in its use. A toothbrushing technique and interdental massage to help eliminate the edematous condition of the gingivae were demonstrated to him. No office treatment was given.

The condition of the gingivae was improved one week later (Fig. 3). The dry, scaly appearance of the lips had improved considerably (Fig. 4). The patient had better appetite and more energy. The pain in his shins was gone, as was the dryness of his skin.

DISCUSSION

While tenderness, swelling, and bleeding of the gingivae have not been described as part of the hypervitaminosis A syndrome, it would seem logical to assume that they would be present along with the other signs and symptoms, since the epithelium is one of the tissues more directly affected by this condition. It is entirely possible that physicians, in their examinations, failed to notice the gingivitis or to attach any significance to it, since gingivitis is so common among persons of all ages.

Also, in this particular case, we see the fallacy and danger of treating the symptoms rather than the cause. The oral findings illustrate the need for a careful history as regards diet and medication, as well as the importance of seeing the patient as a total individual rather than just an oral problem.

SUMMARY

A case of hypervitaminosis A in which a typical marginal gingivitis was part of the syndrome has been presented.

The need for an accurate history and examination is well demonstrated.

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Hypervitaminosis A

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Report of a Case

STANLEY S. BERGEN, JR., M.D.* AND OSWALD A. ROELS, PH.D.†

ALTHOUGH hypervitaminosis A may be encountered fairly frequently in pediatric practice,[1–3] only eight cases have been described in adults.[4–11] The acute form of vitamin A intoxication has been noted in persons ingesting large quantities of polar bear liver[12] or excessively large single doses of vitamin A.[13] Chronic hypervitaminosis A occurs in patients who have received large doses of this vitamin for dermatologic conditions and who have continued subsequent intake without medical supervision, and in food faddists who include large doses of various vitamin preparations in their daily dietary regimens. The present case is an example of the latter.

REPORT OF CASE

A sixty-two year old single white woman (C. F.) was first admitted to St. Luke's Hospital in September 1963 because of stasis ulcers on the lower areas of both legs. The patient stated that she had had dry scaly skin for many years and had been told that she had atopic dermatitis. Stasis ulcers were first noted three years prior to this admission and were severe enough to require the patient's hospitalization elsewhere one and a half years later. Despite continuous local therapy, the ulcers had never healed completely. Eight months prior to this admission, the lower portions of her legs became red and the ulcerated areas began to enlarge. Because of this she was hospitalized elsewhere for three months but the lesions failed to heal. Shortly after her discharge, the condition became more severe and prompted her to visit the outpatient department of St. Luke's Hospital.

Her past medical history disclosed that she was a food faddist who had adhered to a lactovegetarian diet from 1922 to 1941 and from 1960 until the present. She thought that she was "allergic to eggs, meat and fish," but when pressed to describe her reaction to these foods stated that "they don't agree with me because they form gas." The patient had noted weakness and fatigue for many years, and complained of chronic constipation with lower abdominal crampy pain that was partially relieved following bowel movements. She had had dull headaches daily for the last two or three years but associated their occurrence and relief with bowel habits and "successful elimination."

The patient had bilateral shoulder pain and low back pain of five year's duration. Previous x-ray studies of her shoulders and knees revealed evidence of mild to moderate osteoarthritic changes. Three years prior to admission the patient stated that all her body hair had fallen out and the portion that regrew was very sparse.

Physical examination revealed a well developed, poorly nourished woman, of stated age, weighing 103 pounds. Temperature, pulse, respirations and blood pressure were within normal limits. Her hair was very sparse and coarse, with marked thinning in the temporal areas; axillary hair, pubic hair and eyebrows were nonexistent. The patient's skin was pale white, very dry and scaly. The lower portions of her legs were edematous, with moderate erythema and punctate hemorrhagic lesions. The lower medial portion of her left leg contained a 3 by 5 cm. shallow ulcerated area. The entire right leg, from ankle to knee, was scaling with many fissures and small ulcerations that were seeping clear serous fluid. There was an excoriated

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papular rash on both legs extending from just below the knee to the mid-thigh. Ears, nose and throat were normal as were the eyes, including funduscopic examination. There was no venous engorgement or thyromegaly; the heart was of normal size and no murmurs were audible. The lungs were clear and no abdominal abnormality or tenderness was noted. The results of pelvic and rectal examinations were within normal limits. Neurologic examination revealed symmetrically equal hypoactive deep tendon reflexes, normal sensory reaction, motor power and coordination.

Both shoulders and knees were tender to palpation and joint motion, but no gross abnormalities were noted. The patient claimed tenderness upon palpation of her dorso-lumbar spine and noted pain on bending at the waist and on straight leg raising. Pressure over the long bones elicited moderately severe pain.

Laboratory data included a normal white blood cell count and differential, a hemoglobin of 13 gm. per cent. A urinalysis showed a specific gravity of 1.020 and a trace of albumin, it was otherwise within normal limits. Results of Mazzini and cephalin flocculation tests were negative; thymol turbidity was 2.1 units, fasting blood sugar 83 mg. per cent (technicon), total proteins 6.5 gm. with 3.6 gm. of albumin, total cholesterol 212 mg. per cent, serum calcium 9.8 mg. per cent, serum phosphorous 5.0 mg. per cent and alkaline phosphatase 8.8 Bodansky units. Latex fixation titer was less than 1:20; protein electrophoresis revealed a slight increase in gamma globulin and serum transaminase was 62 Sigma units. An electrocardiogram was within normal limits, as were roentgenograms of the gallbladder and the upper and lower gastrointestinal tract. A chest roentgenogram disclosed emphysematous lung fields, arteriosclerotic changes in the aorta and a slightly enlarged heart. X-ray films of the shoulders and knees revealed marked generalized demineralization of all bones with marked osteoarthritis. Roentgenograms of the spine demonstrated kyphoscoliosis with anterior slipping of the seventh cervical and first dorsal vertebrae, collapse of the fifth dorsal, first, second and fifth lumbar vertebrae with marked osteoarthritis.

Shortly after admission, the patient had a spontaneous anterior dislocation of the right humerus which was reduced manually. With local cleansing, and the administration of bacitracin and hydrocortisone ointment, scaling and cracking of both legs seemed to diminish, but the ulcer on the left leg failed to heal. The edema and erythema in the lower extremities subsided with bed rest, and the patient was fitted with a back brace in an attempt to relieve some of the pain associated with her vertebral compression fractures and osteoporosis. Despite repeated discussions with the patient, she refused to change her dietary habits.

In late October the patient was transferred to the Convalescent Unit of St. Luke's Hospital, where these findings were noted, and a small firm mass was palpated in her left breast. The striking association of her physical appearance, dietary habits and clinical condition suggested the possibility of chronic hypervitaminosis A. Analysis of her dietary history revealed an average daily intake as outlined in Table 1.

TABLE 1
Summary of Daily Dietary Intake*

Protein	75 gm. (15%)
Fat	40 gm. (18%)
Carbohydrate	330 gm. (67%)
Vitamin A in food consumed	8,714 I.U. (normal 5,000 I.U.)
Vitamin C in food consumed	34 mg. (normal 95 mg.)

* Total calories 1,978.

The patient stated that she had taken numerous vitamin preparations daily, including the hospitalization period, for at least eight years. These included 33,333 I.U. of vitamin A, 40 mg. of vitamin B_1, and 500 mg. of vitamin C, and were supplemented from time to time by the parenteral administration of vitamin B_{12} and vitamin preparations prescribed and/or administered during hospitalizations.

The serum vitamin A level at this time was 165 μg. per cent (normal 30 to 70 μg. per cent) and serum carotene concentration was 375 μg per cent (normal 100 to 200 μg. per cent). Subsequent laboratory data included a blood urea nitrogen of 11 mg. per cent, serum vitamin C 1.3 mg. per cent (normal 0.4 to 1.5 mg. per cent), prothrombin time 14 seconds (100 per cent activity), protein-bound iodine 10.8 μg. with total iodine of 11.0 μg. and T_3 resin uptake of 1.49 (normal range 0.82 to 1.35) (some of the patient's vitamin preparation contained iodine supplements). Serum triglycerides were 126 mg. per cent, 24 hour urine for creatinine 768 mg. per 24 hour volume (normal 15 to 25 mg. per kg. body weight per 24 hours), creatine 47

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mg. per 24 hours (normal less than 100 mg.) and alpha amino nitrogen 153 mg. per 24 hours (normal 64 to 199 mg. per 24 hours). Spinal puncture revealed clear spinal fluid with pressure of 130 mm. of cerebral spinal fluid. Cell count, protein and colloidal gold uptake were normal; the spinal fluid vitamin A level was zero.

During the patient's hospitalization, a mammogram revealed a small density in the lower margin of her left breast and she was returned to St. Luke's Hospital where a left radical mastectomy was performed with apparent complete removal of an adenocarcinoma. Her vitamin therapy was stopped and over the ensuing two months there was a striking change in the patient's clinical status. The skin cleared, the ulcer on the leg began to granulate for the first time in almost two years, constipation subsided, body hair increased, headaches ceased and the patient's general affect improved. At the present time, although the bone pain has cleared, back pain and shoulder pain remain as the most significant complaints probably due to the compression fractures and osteoarthritis. Serum vitamin A level was 80 μg. per 100 ml. and carotene level 139 μg. per 100 ml. six months after cessation of vitamin A therapy.

COMMENTS

This patient had many clinical symptoms and physical findings suggestive of chronic hypervitaminosis A.[4–11] Although her daily intake of vitamin A may have been less than the minimal value of 50,000 I.U. per day which Stimson[10] considers necessary to cause this clinical condition, it is possible that this patient's neurotic state interfered with her ability to relate to us her actual daily vitamin ingestion. Aside from this supplementation, she was receiving almost twice the daily requirement of vitamin A in her diet.[14] Her skin lesions, sparse hair, refractory stasis ulcers, bone pain, headaches, abdominal pain, constipation and peripheral edema all disappeared entirely or diminished with cessation of excessive vitamin A intake. The serum vitamin A level, which was extremely high when she was first seen, returned toward normal after withdrawal of vitamin A supplementation for six months. The zero vitamin A level in the patient's spinal fluid cannot be evaluated since to our knowledge no previous measurements of this type have been performed. The minimal symptoms of central nervous system involvement that she manifested, compared to those in some of the cases previously recorded,[7,9] may be related to this zero level. There was no evidence of significant muscle wasting as indicated by the relatively normal urinary levels of creatine, creatinine and alpha amino nitrogen.

This is the ninth case of chronic hypervitaminosis A to be reported since Josephs directed attention to this entity in 1944.[1] Some of the cases have been diagnosed by clinical signs alone, while others have been confirmed by the clinical course following withdrawal of vitamin A supplementation. Other cases have been confirmed by the measurement of serum vitamin A and carotene levels.[6,9–11] Unfortunately, because different methods have been used, no comparison can be made of these values. Although the highest serum vitamin A level, was recorded in the case of Soler-Bechara and Soscia,[11] we believe the method employed by one of us (O.R.) is the most specific and accurate one available,[15] and indicates a definitely elevated level.

Due to the lack of awareness of the condition and poor attention to recording dietary histories, in many of the previously recorded cases long periods elapsed before the correct diagnosis was established.[7] This leads us to suspect that many patients, in particular food faddists and many of those diagnosed as being psychoneurotic, may be afflicted with hypervitaminosis A. Clinical expression of this disease is noted in the integument, musculoskeletal system, gastrointestinal tract, central nervous system and hematologic system. Although the onset is variable, it is probable that the excessive intake of vitamin A must persist for from eight to twelve months. Stimson[10] believes that ingestion of 50,000 I.U. of vitamin A a day as supplementation for eighteen months is the minimum requirement for the production of symptoms, whereas Gerber et al.[7] report that at least 2,000,000 I.U. are needed in a single dose to cause acute symptoms.

Patients with hypervitaminosis A can pre-

sent with a wide spectrum of signs and symptoms.[6-11] Fatigue, malaise and lethargy are common presenting complaints and are usually accompanied by one or more of the following: abdominal discomfort, bone and/or joint pain, severe throbbing headaches, insomnia and restlessness, night sweats, loss of body hair and/or brittle nails. Rarer symptoms include constipation, irregular menses and emotional lability. Confirmatory evidence gained from physical examination includes the loss of eyebrows and other body hair; dry, scaly, rough skin with brawny desquamation; peripheral edema with petechial-like lesions; mouth fissures and yellow waxy pigmentation (due to carotenoid deposits) particularly involving the soles, palms and nasolabial folds. Although these patients sometimes have an appearance and history suggestive of hypothyroidism, they often have exophthalmus.[6,16,17] Fundal changes of early papilledema and other signs of increased intracranial pressure have been noted and are probably secondary to increased formation of cerebral spinal fluid.[7] Lymphadenopathy and hepatosplenomegaly have also been observed.[6-10] Abnormal laboratory findings include anemia, hypoproteinemia, hypoprothrombinemia, increased total blood lipids, increased serum alkaline phosphatase and increased urinary calcium excretion.[5]

A low basal metabolic rate is often recorded. No typical bone lesion is demonstrable on roentgenograms to explain the pain and tenderness, although occasionally periosteal overgrowth may be noted.[18]

Differential diagnosis can include almost any chronic debilitating disease or psychoneurosis. Diseases associated with yellowing of the skin, such as Addison's disease, hypothyroidism, jaundice and hemosiderosis, should be considered and almost any type of central nervous system disease can be mimicked by hypervitaminosis A.

The spectrum of this condition and the availability of many vitamin preparations require the physician to maintain a high index of suspicion when confronted with a patient who has an unexplained multiple system disease.[19] Only a complete nutritional history may disclose the patient's underlying process. Treatment consists of the withdrawal of the offending agent and appropriate supportive care as indicated.

SUMMARY

A patient with clinical hypervitaminosis A and elevated serum vitamin A and carotene levels is presented. Many of her signs and symptoms were typical of this entity which was discovered after obtaining a complete dietary history. The patient's condition improved following cessation of vitamin A supplementation.

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Original Communications

Liver Lipids in a Case of Hypervitaminosis A

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BERGEN and Keels have recently summarized the pertinent literature dealing with acute and chronic hypervitaminosis A.[1] The clinical signs and symptoms of toxicity in man have been well documented but there is a sparsity of data on the biochemical effect of excessive ingestion of this vitamin. Since vitamin A is stored primarily in the liver as a lipid-like compound and since it has been incriminated as causing fatty acid infiltration in the reticuloendothelial cells, especially the Kupffer cells of the liver, when consumed in large amounts,[2] it appeared worthwhile to investigate the effects of prolonged ingestion of this vitamin on the various parameters of liver lipids in man. The present case is presented for this purpose.

REPORT OF A CASE

A seventy-nine year old, married, white man was admitted to the University Hospital in October 1964 because of a cerebral vascular accident that occurred on the day of admission. Prior to the present illness, his wife stated that he had been in excellent health. A pertinent fact not recorded in the medical history but known by me was that he had taken 50,000 I.U. of vitamin A daily for the past seventeen years because he thought it was "good for him." A review of his dietary habits revealed a balanced food intake with no evidence of food faddisms or excessive intake of those foods high in vitamin A or its provitamin. A careful review of the recorded history and physical examination revealed none of the classic signs and symptoms of vitamin A toxicity. The patient died on the eighth hospital day. Postmortem examination confirmed the clinical diagnosis of cerebral vascular accident and arteriosclerotic disease. The liver showed no gross or microscopic evidence of disease.

CHEMICAL METHODS

Immediately after death the liver was removed, washed free of blood and sectioned for chemical analyses. Lipid was extracted with chloroform-methanol.[3] The lipid extract was analyzed for vitamin A content[4] and the various lipid components were separated by means of silicic acid chromatography.[5] Due to the contamination of the cholesterol ester with vitamin A, it was necessary to determine the quantity of this esterified sterol by the Leiberman-Burchard reaction.[6] The types of fatty acids esterified with the various lipid fractions were determined by gas chromatography.[7]

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RESULTS

The liver weighed 1,375 gm. and contained 5.40 gm. of vitamin A. The concentration of the other lipid components expressed on the basis of grams per 100 grams of fresh liver were 3.86 (total lipid), 0.86 (neutral fat), 1.56 (phospholipid), 0.03 (cholesterol ester) and 0.15 (free cholesterol).

The major fatty acids associated with triglycerides were palmitic (48.2 per cent), stearic (12.4 per cent), oleic (27.5 per cent), linoleic (6.3 per cent) and arachidonic (3.4 per cent). The distribution of fatty acids in the phospholipid fraction was palmitic (32.8 per cent), stearic (21.1 per cent), oleic (18.4 per cent), linoleic (18.7 per cent) and arachidonic (9.0 per cent).

Due to the large amount of vitamin A ester present in the liver it was not possible to purify the cholesterol ester fraction. Therefore, the fatty acids associated with cholesterol were not measured. It was possible, however, by silicic acid chromatography[8] to isolate a 97 per cent pure vitamin A ester fraction which contained 68 per cent palmitic, 10.7 per cent stearic, 13.6 per cent oleic and 7.6 per cent linoleic acid.

COMMENTS

The total amount of vitamin A stored in this liver was approximately forty times the normal amount found in livers from elderly subjects[9] and the concentration was approximately half of that reported for polar bear liver.[9] The total amount of this vitamin stored represents about 5 per cent of the total amount ingested (excluding dietary source) over the seventeen year period.

It was unfortunate that blood samples and sections from other tissues were inadvertently lost at the time of autopsy. It would have been interesting to have noted the concentration of vitamin A in tissues not primarily concerned with storage.

From a nutritional point of view, it is interesting that the ingestion of this excessive amount of vitamin A for seventeen years did not produce any well recognized signs and symptoms of toxicity. This finding would suggest that vitamin A toxicity is perhaps related as much to the individual's susceptibility or resistance to toxicity as to the amount ingested. Certainly on a total intake basis this subject had consumed a sufficient amount of vitamin A to have produced toxic effects. Perhaps, however, toxicity did not develop due to an acquired tolerance or a compensation which may have developed because of the prolonged, excessive ingestion of this vitamin. Until we understand the metabolic effects and metabolism of this vitamin more thoroughly, the reason for differences in individual susceptibility will remain unanswered.

The storage of this excessive amount of vitamin A appeared to have had little or no effect on the concentration or partitioning of the various liver lipids. The total lipid concentration and the amount of the various lipid fractions in this case compare favorably with reported values for normal human livers.[10] Therefore, these findings do not support the view that hypervitaminosis A is associated with an increase in liver lipid.[9]

The storage of excessive amount of vitamin A, however, does appear to influence the composition of liver fatty acids. A comparison of the fatty acids found in the livers of normal elderly persons[11] with those obtained from this liver revealed that (1) the major fatty acid component of this hypervitaminotic liver was palmitic acid, in counter distinction to oleic acid in a normal liver; (2) the increase in concentration of vitamin A was associated with an increase in the percentages of palmitic and stearic acids in liver triglycerides; and (3) the normal percentages of the various fatty acids associated with the phospholipid fractions were not affected by the increased concentration of liver vitamin A.

The increase in the concentration of palmitic acid found in this liver is no doubt due to the large amount of vitamin A esterified with palmitic acid.[9,12] It is interesting to note, however, that about 20 per cent of the vitamin ester was in combination with unsaturated fatty acids. In general the major fatty acids esterified with vitamin A were palmitic, stearic and oleic.

The biochemical significance of esterifying vitamin A is unknown. It has been postulated that the esterification process may be the

liver's way of detoxifying excessive amounts of vitamin A.[9] This question will remain unanswered until the "physiologic active" form of vitamin A is established.

SUMMARY

The ingestion of 50,000 I.U. of vitamin A by an elderly adult for seventeen years did not result in obvious signs and symptoms of vitamin A toxicity. The total liver contained 5.4 gm. of vitamin A. The lipid content was within normal limits. Palmitic acid was the major fatty acid in the various lipid fractions isolated.

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lone being capable of modifying the initial response and the vehicle being necessary to maintain it so.

Despite the application of steroid medication, the phenomenon of tissue repair was not hindered and the deposition of reparative dentin occurred on schedule.

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A STUDY OF THE EFFECTS OF HIGH DOSES OF VITAMIN A ON ORAL LEUKOPLAKIA (HYPERKERATOSIS), INCLUDING TOXICITY, LIVER FUNCTION AND SKELETAL METABOLISM

SOL SILVERMAN, JR., EUGENE EISENBERG, AND GRETE RENSTRUP

Control of oral leukoplakia (hyperkeratosis) is an unsolved problem because it cannot always be reversed or diminished by removing irritants, the location and extent of the lesions do not always allow surgical or diathermic removal, and some leukoplakias are associated with development of squamous carcinomas.[1, 2] For the purpose of this study, leukoplakia (hyperkeratosis) is defined as any white patch or plaque on the oral mucous membrane that cannot be removed by scraping, cannot be reversed by removing obvious irritants, cannot be classified clinically or microscopically as another diagnosable disease, and is histologically characterized by hyperkeratosis without cellular dysplasia.

Two previous reports[3, 4] have described either complete or partial and temporary remissions of oral leukoplakia in 22 of 35 patients who dissolved troches containing 450,000 to 750,000 units of vitamin A in the mouth daily for two to six weeks. Serum vitamin A levels in these subjects showed temporary increases which could not be correlated with lesion response. Histologic examinations revealed decreases in the thickness of the stratum corneum and consistent tendencies towards lesser degrees of cornification. Exfoliative cytologic studies showed decreases in both cytoplasmic acidophilia and denucleation. Half of the patients also displayed toxic effects consisting of dryness, itching and scaling of the skin. These effects disappeared shortly after vitamin A administration was discontinued. The purpose of this investigation was to acquire more information on the clinical, histologic and metabolic effects of hypervitaminosis A in human subjects.

MATERIALS AND METHODS

Six human adults with oral leukoplakia were used for this study. All but patient P. B. had previously taken high dosages of vitamin A for their oral lesions: 1) D. C., who had a daily intake varying from 300,000 to 750,000 units for 15 months, stopped three months prior to this investigation; 2) A. C., who had a daily intake of 750,000 units for three weeks, stopped five months prior to this investigation; 3) D. M., who had a daily intake of 75,000 units for 1½ years, stopped 12 months prior to this study; 4) L. C., who had a daily intake ranging from 300,000 to 750,000 for ten weeks, stopped 15 months prior to this investiga-

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TABLE 1

Leukoplakia and serum response to 600,000 U vitamin A daily after 4 weeks ingestion

Patient	Age	Sex	Mucosal Site	Resolution	Serum Vitamin A* (I.U. per 100 ml)		Serum Carotene* (μg%)	
					Control	Vit. A	Control	Vit. A
L. C.	75	F	Dorsal Tongue	Partial	69	514	203	222
D. C.	59	M	Buccal	Complete	26	267	58	27
F. B.	46	F	Dorsal Tongue	Partial	58	395	113	84
A. C.	69	F	Hard Palate	None	122	476	149	163
D. M.	33	F	Ventral Tongue	Complete	78	1632	93	141
P. B.	63	M	Buccal	Partial	114	—	64	—

* Normal values: Vitamin A: 65–275 I.U. per 100 ml; Carotene: 50–300 μg%.

FIG. 1. A. Patient D. M. with leukoplakia (hyperkeratosis) of the ventral tongue and floor of the mouth before vitamin A administration. B. During the 5th week of vitamin A administration, the mucosa clinically appeared to be normal and histologic specimens indicated an epithelial change from hyperorthoketatosis to normal.

tion; and 5) F. B., who had a daily intake varying from 450,000 to 600,000 units for five months, stopped 18 months prior to this investigation. The patients were hospitalized for six-day study periods before and during vitamin A administration. Each patient had the following studies: 1) complete medical and physical examination; 2) complete blood count and urinalysis; 3) bromsulphalein excretion (BSP) and serum glutamic oxaloacetic transaminase (SGOT); 4) tests of calcium and phosphorus metabolism and kinetics of bone-seeking mineral using stable strontium as a tracer[9]; 5) serum vitamin A and carotene assays[10]; 6) complete roentgenographic survey of the skeleton; and 7) biopsies of the oral leukoplakia and adjacent normal appearing mucosa. After completing the baseline examinations, vitamin A troches* (75,000 units each) were prescribed to be dissolved eight per day (600,000 units) for a period of four weeks. The patients were then rehospitalized; and while the vitamin A administration was continued for a fifth week, the above examinations were repeated.

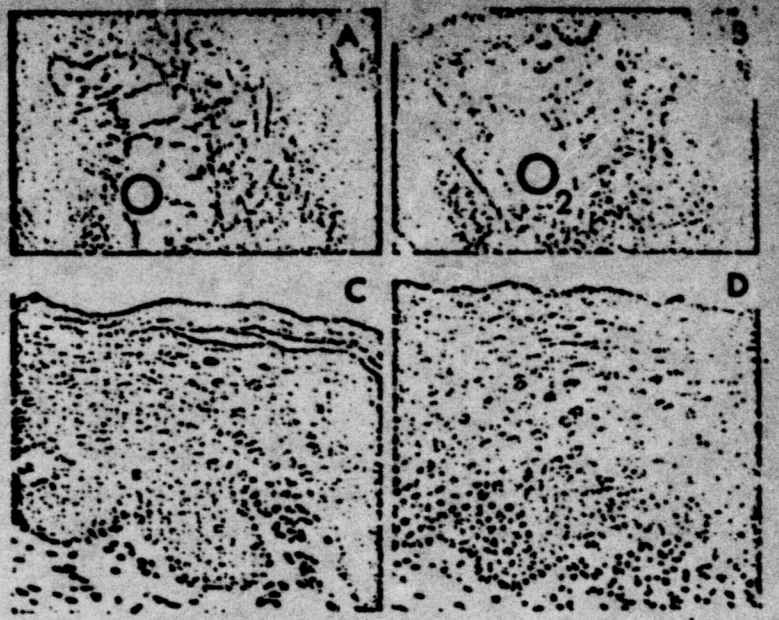

FIG. 2. Patient F. B. with leukoplakia (hyperkeratosis) of the dorsal tongue. A. Lesion before vitamin A administration. Encircled area 1 indicates biopsy site (5 mm punch). B. Partial remission of the leukoplakic lesion during the 5th week of vitamin A administration. Encircled area 2 indicates biopsy site (5 mm punch). Note multiple areas of lesser degrees of cornification. C. Biopsy specimen from area 1, fig. A, demonstrating hyperorthoketatosis before vitamin A administration (orig. mag. × 220). D. Biopsy specimen from area 2, fig. B, demonstrating hyperparakeratosis during vitamin A administration (orig. mag. × 220).

Findings

Response of leukoplakia. Table 1 lists the changes in the oral leukoplakia and alterations in serum total vitamin A and carotene following vitamin A ingestion.

* Vi-Dom-A tablets, Dome Chemicals, Inc., N. Y.

There were two complete responders (fig. 1) and three partial responders (fig. 2); this distribution of remissions is similar to our previous findings.

Serum vitamin A and carotene. As shown in Table 1, fasting serum vitamin A concentrations increased from 4 to 21 times control levels after four weeks of vitamin A ingestion. Serum carotene levels in five of the six patients were all within a normal range and were not altered in any apparent pattern by increased serum vitamin A levels.

Histologic changes. Table 2 describes the histologic changes observed in the leukoplakic specimens before and during vitamin A ingestion. Serial sections were examined from each biopsy, comparing vitamin A and control specimens with each other as well as with a specimen from adjacent clinically normal appearing mucosa. The microscopic changes of the leukoplakias were consistent with the clinical responses (fig. 2). Adjacent clinically normal appearing mucosa showed neither histologic abnormalities nor interval changes. The vitamin A specimen from patient D. C., who had complete remission of his leukoplakia, displayed an apparent increase in the observed number of mitotic figures.

Toxicity. Table 3 lists the effects displayed by the patients during the fourth and fifth weeks of vitamin A administration (fig. 3). All of these signs and symp-

TABLE 2

Histologic responses of leukoplakias after 4 weeks of 600,000 U vitamin A taken daily

Patient	Keratin*		Prickle Cell Layer		Inflammation	
	Control	Vitamin A	Control	Vitamin A	Control	Vitamin A
L. C.	Hyperortho	↓ Hyperortho	Normal	Normal	None	None
D. C.	Hyperpara	Normal	Hyperplasia	Atrophy	Marked	Marked
F. B.	Hyperortho	Hyperpara	Normal	Normal	Slight	Slight
A. C.	Hyperortho	Hyperortho	Normal	Normal	None	None
D. M.	Hyperortho	Normal	Normal	Normal	Slight	Slight
P. B.	Hyperpara	↓ Hyperpara	Hyperplasia	Hyperplasia	Moderate	Moderate

↓ = Decreased.

* Hyperparakeratosis: A pathologic condition in which the outer cells and cell layers are flattened, contain pyknotic nuclei and exhibit a marked acidophilia. In areas where parakeratosis normally occurs, it has to exceed the expected thickness to be called hyperparakeratosis.

Hyperorthokeratosis: A pathologic condition in which the superficial layers of the epithelium are cornified, containing no nuclei and appearing homogeneous and strongly acidophilic. In areas where orthokeratosis normally occurs, it has to exceed the expected thickness to be called hyperorthokeratosis.

TABLE 3

Toxic effects after 4 weeks of daily ingestion of 600,000 U vitamin A

Patient	Dry Skin	Pruritus	Rash	Brittle Nails	Bone Pain	Headache	Disorientation	Cheilitis	Myositis	Anorexia	Constipation	Nausea & Vomiting	Urinary Retention	Photosensitivity
L. C.	X	X	X		X			X			X			
D. C.	X	X	X		X	X			X					
F. B.	X			X										
A. C.	X	X		X										
D. M.	X	X												
P. B.	X	X	X			X	X	X		X		X	X	X

FIG. 3. Toxic manifestations of patient P. B. during 5th week of vitamin A administration. A. Angular cheilitis. B. Rash and dry scaling on left arm. C. Biopsy specimen of the skin of the left forearm demonstrating a hyperkeratosis consistent with a non-specific dermatitis (orig. mag. × 125).

tosis disappeared within 20 days after discontinuing vitamin A. Photosensitivity demonstrated by patient D. M. and urinary retention afflicting patient P. B. have not been reported previously.

Liver function. Table 4 illustrates an effect of hypervitaminosis A on liver function as reflected by elevation of BSP in three of five patients, and small rises in SGOT in three patients. Liver function tests after discontinuing vitamin A returned to pretreatment levels, except in patient D. C. in whom the BSP returned towards normal. Alkaline phosphatase does not appear to be affected. There were no clinical symptoms or signs of liver dysfunction.

TABLE 4
Effects of vitamin A on liver function studies

Patient	Bromsulphalein Excretion (BSP)			Serum Glutamic Oxaloacetic Transaminase (SGOT)			Alkaline Phosphatase (SJR Units)		
	Control Before	Vitamin A	Control* After	Control Before	Vitamin A	Control* After	Control Before	Vitamin A	Control* After
L. C.	—	—	8%	—	30	13	—	6.7	4.6
D. C.	8%	31%	21%	18	48	29	5.6	8.9	8.0
F. B.	6%	14%	4%	12	14	—	3.9	4.6	—
A. C.	9%	13%	—	15	17	—	5.1	4.8	—
D. M.	1%	2%	—	11	8	—	4.3	4.1	—
P. B.	4%	9%	8%	9	28	—	4.7	7.8	—

Normal values: BSP: 5% retention (45 min); SGOT: 8 to 40 Units; Alkaline Phosphatase: 2.2 to 8.6 SJR Units.
* 2 months after discontinuing Vitamin A.

TABLE 5
Effects of vitamin A on calcium and phosphorus metabolism and strontium kinetics (600,000 U daily for 4 weeks)

Patients	Strontium Kinetics				Calcium		Phosphorus	
	Miscible pool (liters)	Bone deposition rate (liters/day)	Urinary excretion rate (liters/day)	Fecal excretion rate (liters/day)	Serum (mEq/liter)	Urinary (mEq/day)	Serum (mg%)	% Tubular reabsorption of phosphate
L. C.								
Control	35.9	7.2	1.7	0.24	4.75	4.4	3.5	92
Vit A	35.4	7.5	2.2	0.27	4.73	4.1	2.8	89
D. C.								
Control	48.7	9.0	4.6	0.42	4.45	12.8	3.0	83
Vit A	50.3	6.8	5.1	0.43	5.15	12.3	3.3	81
F. B.								
Control	35.4	4.3	2.2	0.48	4.45	3.5	3.7	88
Vit A	28.2	4.6	1.6	0.51	4.95	2.7	3.7	78
A. C.								
Control	43.4	7.8	3.8	0.50	4.75	5.8	3.9	88
Vit A	38.4	7.1	3.1	—	4.90	5.0	3.7	90
D. M.								
Control	31.8	6.0	2.8	0.2	4.95	5.2	3.5	89
Vit A	28.9	5.5	2.2	0.1	5.25	4.2	2.7	84
P. B.								
Control	41.3	5.4	3.9	—	4.30	6.8	3.1	81
Vit A	39.9	7.5	4.2	—	4.45	7.4	3.3	79

Normal Values: Pool: 35 to 55 L; Bone deposition: 8 to 11 L/D; Urinary excretion rate: 2.9 to 5.9 L/D; Fecal calcium: 0.5 to 1 L/D; Serum calcium: 4.80 to 5.65; Urinary calcium: 2 to 10; Serum phosphorus: 2.6 to 4.3; Tubular reabsorption phosphorus: 80 to 90.

TABLE 6
Effects of vitamin A on serum ascorbic acid and thyroid hormone

Patient	Ascorbic Acid		Butanol Extractable Iodine	
	Control	Vit A	Control	Vit A
D. C.	0.5	0.2	3.2	2.4
F. B.	2.1	0.7	3.8	2.1
D. M.	0.1	0.1	3.2	3.4
P. B.	1.6	1.4	3.9	3.7

Normal Values: Ascorbic acid: 0.5-1.5 mg%; BEI: 2.2-5.6 mg%.

Calcium dynamics. Table 5 lists the data for the effects of vitamin A on calcium and phosphorus metabolism and strontium kinetics. Serum calcium, phosphorus and percentage tubular resorption of phosphate were normal and did not significantly change during vitamin A administration. Patients F. B. and D. M. had small miscible pools; and all bone deposition rates, except for the control study in patient D. C., were below normal. There were no significant changes in any of the kinetic measurements induced by high doses of vitamin A. Bone surveys showed some degree of osteoporosis, and there was no evidence of change at the end of vitamin A administration.

Other examinations. The complete blood counts, urinalyses, serum creatinines, serum proteins, fasting blood sugars and electrocardiograms were all either within normal limits or showed no significant interval changes. In four patients tested, hypervitaminosis A had no specific or consistent influence on circulating thyroid hormone or serum ascorbic acid (table 6).

DISCUSSION

Vitamin A studies on keratinization were first stimulated by observations that in some vitamin A-deficient animals mucous-type epithelia converted to a keratinizing type[37]. These findings subsequently prompted the thought that vitamin A in certain forms and concentrations may inhibit or alter hyperkeratosis. This has now been confirmed in oral leukoplakias[19, 22, 31, 37, 46, 49, 51], certain dermatologic disorders[4, 13, 41] and in a variety of animal experiments[11, 20, 37] and tissue culture studies[10, 11, 23, 32]. Although the mechanisms of action of vitamin A on keratinization are unknown,[10, 23] *in vitro* and *in vivo* studies have suggested the following possibilities: 1) alteration of sulfur metabolism which may interfere with keratin formation;[2, 11, 14, 15, 50, 59] 2) the release of a lysosomal protease that may break down keratin or inhibit its precursors;[6, 7, 23] and 3) an increased mitotic index[20, 42, 46] which may alter epithelial maturation precluding keratin formation.

No matter what the basic mechanism of action might be, our previous stud-

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ies[47, 48] have shown that the effect on oral leukoplakia appears to be dependent upon undetermined local factors and troche type administration and that responsiveness did not correlate with absolute or relative serum levels of vitamin A. On the other hand, Johnson, Ringsdorf and Cheraskin in 1963[49] reported that systemic administration induced remission in some oral leukoplakias. Wulf in 1957[50] also made this observation. In our previous series,[47] two patients who were complete responders to oral troches (600,000 U per day for two weeks) demonstrated no response to similar dosages in capsule form of vitamin A acetate. Our previous studies also show the effect not to be dependent upon the type of leukoplakia (hyperorthokeratosis or hyperparakeratosis), age or intraoral site. One observation in our previous studies had been that all complete responders (9 of 35 patients) were males; however, of the partial responders, 8 of 13 were females, whose ages ranged from 37 to 73. We had speculated that this observation indicated a possible sex difference, which could be related to antagonism between estrogen and vitamin A[26, 48]. However, based on the complete response of patient D.M., a 33-year-old female, it appears that there may be no sex response difference.

In all instances, remissions appear to be maximal in two weeks; and, upon withdrawal of vitamin A, the lesions recur in their original form in approximately two weeks. Of interest, in three patients studied with hyperkeratosis associated with lichen planus, the remissions were of longer duration, and the lesions observed for more than one year have not returned to their original intensities of keratosis. Administration of placebos in some of the leukoplakic complete responders has not induced any remissions.

Serum Vitamin A Levels

As indicated in Table 1, the control serum levels of vitamin A were essentially all within the normal range, except for patient D. C., whose value was low. Wahi and associates in 1962[34] observed that patients with oral leukoplakia had a deficiency of vitamin A which was even greater in patients with oral cancer. These results are based on studies of serum vitamin A levels in 60 normal, 123 oral leukoplakic and 333 oral carcinoma patients at the Radium Institute of S.N. Hospital, Agra, India. The values among the three groups were 160 ± 25, 121 ± 19 and 102 ± 14 I.U. vitamin A per 100 ml serum, respectively. Although these results do not indicate a true vitamin A deficiency nor prove the proposed relationship, it is of interest that patient D. C., who had the lowest control serum level of vitamin A in our group, has had four intraoral carcinomas associated with his leukoplakias.

In a preliminary evaluation of Wahi's observations, fasting levels of serum vitamin A were determined on 17 San Francisco Medical Center patients with oral carcinoma, 11 with oral leukoplakia and 12 without evidence of oral disease (table 7). The serum specimens were frozen and analyzed as two evenly divided batches by the same laboratory, utilizing the activated glycerol dichlorohydrin method[51]. Although the small number of patients does not permit any definitive conclusions, the findings indicate no basis to assume a correlation in our subjects between low serum vitamin A levels and oral leukoplakia or oral cancer. The significance of subnormal vitamin A serum levels in each group is unknown, since the patients had adequate diets and none displayed clinical evidences of any vitamin deficiencies. However, it should be pointed out that the normal values quoted are taken from the literature and are not established on a large normal series by this laboratory. It must also be remembered that circulating total vitamin A has an extremely large normal range and that values for individuals as well as among patients may fluctuate quite widely[17, 25, 44, 52, 53]. Furthermore, little is known about the relationship between circulating vitamin A, tissue levels and biologically active forms[8, 22, 40, 45, 61].

Table 7

Group control values of serum vitamin A

Group	No.	Average age	Mean serum Vit. A I.U./100 ml	Standard deviation	Range
Normals	12	61	95	±53	8-178
Oral leukoplakia	11	59	91	±65	17-231
Oral cancer	17	59	52	±45	8-161

Hume's classical study[20] attempting to create vitamin A deficiency in human subjects pointed out the technical variabilities and inconsistencies in serum vitamin A determinations. Also, even after significantly lowering serum vitamin A levels in his subjects, he found a lack of clinical effects. However, his experiments were conducted on young males during a period of time less than two years.

Toxicity

All six patients showed some toxic effects which completely disappeared within three weeks after discontinuing the vitamin A ingestion. Of the 35 patients previously given excessive amounts of vitamin A[47, 48], 18 had toxic manifestations. The appearance and magnitude of the toxicities could not be correlated with absolute or relative serum vitamin A levels. Possibly they are related to unknown individual tissue specific metabolic factors, variable critical blood levels or exposure time. It is of interest that patient D. C., who had previously been subjected to high dosages of vitamin A over a period of two years, never before had demonstrated any toxic signs or symptoms. Serum vitamin A can be steadily lowered to preexisting control levels by reducing the dose or by discontinuing the drug.

In the 35 patients previously studied, the following incidences of signs and symptoms were recorded: 14 with dry skin, pruritus or rash; 4 with angular cheilitis; 3 with constipation; 2 with mucositis; periorbital swelling in 2 and 1 with headache. In the other studies on oral leukoplakia utilizing high dosages of vitamin A,[10, 31, 49, 50] no well-defined toxic manifestations were reported. Even in Burgoon's dermatologic study[4] in which 16 adults were given 400,000 to 1,000,000 units of vitamin A daily for one to eight months, pruritus was noted in only one patient.

units vitamin A acetate to 16 patients aged 61 to 80 daily for six months. Serum vitamin A increased in all patients and returned to pre-vitamin A levels within three months after discontinuing the vitamin. No toxic effects were reported.

Raaschou-Nielsen[30] and Stimson[31] in a review of the literature and case reports relate chronic intoxications in nine adults from vitamin A intake ranging from 100,000 to 600,000 units per day during periods varying from 2 to 102 months. Signs and symptoms reported included bone and joint pains, fatigue and insomnia, cheilitis, anorexia, weight loss, rash, pruritus, alopecia, bleeding and hepatomegaly. A recent report by Soler-Berbara and Socias[32] describes chronic hypervitaminosis A in a 39-year-old female who ingested approximately 75,000 to 150,000 units of vitamin A daily for eight years, with an increase during the last six months to 375,000 units per day. Findings included fatigue, weight loss, bone and joint pain and tenderness, loss of hair, pruritus, dry skin, rash, hepatosplenomegaly, anemia and headaches. Her initial fasting serum vitamin A was 874 mg per 100 ml. Seven weeks after discontinuing vitamin A, her blood level was reduced to 327 mg per 100 ml. By this time, only complaints of alopecia and minimal leg pain were recorded. The high vitamin A serum levels after seven weeks abstinence were probably due to slow liver release of stored vitamin A[10]. But it is of interest to note that, as in two of our patients previously studied, most toxic effects had disappeared even though an elevated serum vitamin A level persisted.

Liver Function

Since vitamin A is chiefly stored and metabolized in the liver[10, 33], one might expect excess dosages of vitamin A to alter liver function. This assumption is confirmed by the finding of BSP retention during vitamin A administration. The alteration appeared to be of a temporary nature. Liver function tests improved after discontinuation of vitamin A, and in three patients they returned to within normal limits. In the youngest patient (age 33) who had the highest serum vitamin A level, liver function was essentially unaltered.

No jaundice or hepatomegaly was seen. In other case reports,[30, 31] hepatomegaly has been reported as a frequent occurrence in chronic hypervitaminosis A. In the case recently reported by Soler-Berbara[32], the patient had hepatosplenomegaly, elevated BSP retention, elevated alkaline phosphatase, hypoprothrombinemia and hypoproteinemia. A liver biopsy and serum transaminase levels were normal. Anderson and Soley in 1938[1] demonstrated abnormal liver function by the Rose-Bengal test in eight of nine patients with carotenemia. Palotta and Krause[34] reported no changes in prothrombin or alkaline phosphatase after administering 100,000 units vitamin A acetate daily for six months to their 16 geriatric patients.

Calcium Dynamics

Vitamin A deficiencies in animals alter bone maturation and growth. In giving excess amounts of vitamin A to rats and guinea pigs, Wolbach[35] demonstrated an accelerated remodeling of bone and the production of fractures. Leaver and Trifitt[36] showed that hypervitaminosis A in rat weanlings produced significantly depressed serum citrate and extremely fragile bones. Histologically, they showed that there were numerous osteoclasts in certain areas. In an opposite type of study in vitamin A deficient rats, Frandsen[37] demonstrated that osteoclastic activity was suppressed or entirely absent as evidenced by the failure of remodeling resorption of immature bone formed in the sockets left by extracted teeth and by the failure of remodeling of the tibial shafts. Clark and Smith[3] have shown that excessive amounts of vitamin A administered to rats accelerate bone remodeling as reflected by increased excretion of calcium and phosphorus. They found that in these animals the ash content of bone remained normal, but there was a loss of collagen and mucopolysaccharide as measured by hydroxyproline and hexosamine. Berdjis[3] has stated that excessive intake of vitamin A or parathyroid hormone in animals produce a similar demineralizing action on bone. In adult human subjects, hypervitaminosis A has been shown to induce bone and joint pain. In children, excessive vitamin A may cause painful hypercalcemia[38] and inhibition of bone growth with premature closure of epiphyses[39].

From these observations, it has been assumed that excessive amounts of vitamin A in human adult subjects could alter bone metabolism and produce pathologic changes. The results from tests of calcium and phosphorus metabolism, strontium kinetics and roentgenographic findings indicate that large dosages of vitamin A for short periods of time do not significantly affect bone metabolism in adults. The radiographic evidence of osteoporosis associated with a low bone deposition rate confirms our previous report[9] of decreased bone deposition rate in patients with postmenopausal or senile osteoporosis.

Ascorbic Acid

It has been shown in animals with experimental hypervitaminosis A that serum ascorbic acid levels were low and that there were decreased amounts of ascorbic acid in the adrenals and liver[40, 41]. This effect has not been demonstrated in humans although it has been cited as a possible related factor in some patients with hypervitaminosis A who have demonstrated skin rash and capillary fragility. None of our patients has demonstrated bleeding tendencies or petechiae. Serum ascorbic acid levels, which do not always reflect the state of vitamin C stores, did not show a consistent or revealing interval change in four of the patients so studied.

Thyroid Function

Several reports in the literature indicate an antagonism between high dosages of vitamin A and thyroid status. Logan[42] demonstrated reduced I^{131} uptake after daily ingestion of 50,000 units of vitamin A for three or more weeks; and Anderson and Soley[1] showed that eight of nine patients with carotenemia had subnormal basal metabolic rates. Sadhu[41, 43] demonstrated in rats that excess vitamin A depressed BMR, reduced thyroid weight, depressed thyrotropic hormone and antagonized effects of thyroxine administration. Soler-Berbara[32] reported borderline low I^{131} uptake, PBI and BMR values on their patient with hypervitaminosis A. Since two of our patients had no change in BMR, two had only a slight

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and none had clinical evidence of hypothyroidism, the results of basal metabolic

evidence of hypothyroidism induced by vitamin A therapy, our study indicates that the antagonism is neither predictable nor constant. Two patients from our previous series also demonstrated normal BEI values while on vitamin A, 600,000 units daily for six weeks. Patient F. B. had a normal I^{131} uptake which showed no interval change while on vitamin A.

Summary

Previous studies have demonstrated the antagonistic effects of large dosages of vitamin A on oral hyperkeratoses. To compare clinical, histologic and metabolic effects, six adults with oral leukoplakia (hyperkeratosis) were studied before and during vitamin A administration. The subjects dissolved in their mouths troches containing a daily total of 600,000 units vitamin A each day for five weeks. Clinical and laboratory examinations were performed before vitamin A administration and during the fifth week of study. Findings showed: 1) complete remission of leukoplakia (hyperkeratosis) in two patients and partial remission in three; 2) serum vitamin A levels increased 4 to 21 times control values; 3) clinical remissions were reflected microscopically by diminution or absence of hyperkeratosis; 4) some toxic effects in all patients, the most frequent being dryness, itching and scaling of the skin; 5) altered liver function in five of six patients as measured by BSP and SGOT determinations; 6) no abnormalities or interval change in calcium dynamics as measured by calcium and phosphorus metabolism and strontium kinetics; 7) no significant interval changes in complete blood count, urinalysis, electrocardiogram, skeletal survey, butanol extractable iodine or serum ascorbic acid levels; and 8) return to control status within three weeks after discontinuing vitamin A ingestion, including recurrence of leukoplakic lesions.

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by an ophthalmologist in another city. For the last three years he had been free of attacks—and not playing in dance bands very often. In December, 1955, he had busy days selling and worked most evenings with dance bands. He also had a 30-mile drive in traffic to and from work. I first saw him December 13th, during an attack.

Examination showed: O.S., mild injection, tension 46 mm. Hg, corneal edema, deep anterior chamber. In spite of glycerine being employed no keratic precipitates were seen. Pilocarpine (four percent) was given. The tension fluctuated between 31 and 24 mm. Hg for 10 days and a few fine keratic precipitates were seen. Suddenly the tension fell to 12 to 14 mm. Hg with disappearance of symptoms and the few fine keratic precipitates. The fields were normal. The tension did not rise when pilocarpine was stopped and a dark-room test was negative. Pilocarpine (two percent) night and morning was prescribed.

On February 15, 1957, there was a recurrence of halos in spite of using pilocarpine. This attack followed one and one-half hours after a car accident. He had used pilocarpine drops several times before I saw him. O.S. showed mild injection, no corneal edema, no keratic precipitates, and a tension of 25 mm. Hg. A few fine keratic precipitates were seen two days later. The attack was completely over in a week. No posterior synechias formed. Following this attack the patient has used no drops and the tension has remained between 14 and 18 mm. Hg. He presented with another attack on May 23, 1958, seeing halos in O.S. There were three fine keratic precipitates; tension 37 mm. Hg. He admitted worrying about a possible change of job. On May 26th, tension was: O.S., 30 mm. Hg, no keratic precipitates; May 30th, O.S., tension 15 mm. Hg. No attacks have occurred since then.

Summary

Glaucomatocyclitic crises are briefly reviewed, classified, and described by Posner and Schlossman's criteria. The treatment and differential diagnosis are summarized. A case is presented which suggests that nervous tension may be an etiologic factor.

622 Medical-Dental Building (1).

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VITAMIN-A INTOXICATION

Charles A. Turtz, M.D.
and
Arnold I. Turtz, M.D
New York

The use of vitamin A in the treatment of acne has long been established. An occasional case of intoxication has been reported in the literature.*

Case report

A 17-year-old boy consulted us in January, 1958, and gave a history of headaches, blurred vision, and

* Oliver, T. K., Jr., and Havener, W. H.: Eye manifestations of chronic vitamin-A intoxication. A.M.A. Arch. Ophth. 60:19-22 (July) 1958.

ONLY COPY AVAILABLE

...ional attacks of diplopia. This was accom-...ied by general malaise and pains in the joints. ...e eye symptoms had been present one week prior ...o his visit. He was tall, and thin and appeared dis-...raught. His visual acuity was 20/50, R.E.; 25/30, L.E. Lids were negative and hemic content was good. There was no muscle imbalance. Slitlamp microscopy revealed no pathologic condition in the cornea or lenses. Examination of the fundi revealed small discrete superficial hemorrhages throughout the retina of both eyes but more marked in the right. The appearance of the vascular tree was normal. There was early edema of the left disc.

On further questioning we were told he had been taking 200,000 units of vitamin A daily for 18 months for acne.

Vitamin A was discontinued. Symptoms gradually disappeared and within 10 days vision returned to 20/25 in each eye, the edema of the left disc subsided, and only an occasional discrete hemorrhage toward the periphery remained.

Comment

In addition to the symptoms and clinical signs in our case, vitamin-A intoxication can produce exophthalmos, increased intracranial pressure with chocked discs, loss of hair, enlarged spleen and liver, skin rash with desquamation and cutaneous pigmentation.

525 Park Avenue.

CROSS-ACTION NEEDLE HOLDER*

Robert E. Bartlett, M.D.
Los Angeles, California

The cross-action lens capsule forceps has come the instrument of choice in its line. requires only a light grasp by the operator ring the delicate maneuver of delivering lens, and the jaws of the instrument can ily be opened without shifting the posi-n of the fingers. The same reasons ompted me to design a cross-action needle der.

The cross-action needle holder has be-

Fig. 1 (Bartlett). Design of cross-action needle holder.

come practical only since the advent of the newer type sharper ophthalmic needles. Too great a spring action would be required to grasp a dull needle firmly and push it through the cornea. This in turn would require too much force by the operator to open the jaws to release the needle.

The strength of the spring of the present instrument is delicately balanced to hold the needle without rotation or sliding during corneal or scleral surgery. Yet it is not so strong that the needle cannot be released without undue effort. Figures 1 and 2 show its general design. It is slightly larger than the Paton and slightly smaller than the Castroviejo needle holder, measuring 12.5 cm. in length. Its design permits it to be held in

Fig. 2 (Bartlett). This view illustrates a way of holding the instrument which is particularly convenient in certain circumstances.

*From the Department of Ophthalmology, Wadsth Hospital, Veterans Administration Center, the Department of Ophthalmology, University California Medical Center at Los Angeles. This ...ument is available at Storz Instrument Com-, Saint Louis, Missouri.

two ways (figs. 1 ...trated in figure ... in certain circum... scleral sutures p... instrument is held ... the jaws conven... lows the surgeon ... posteriorly witho... an awkward posit...

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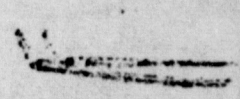

Fig. 1 (Guerry). Re...

HYPERVITAMINOSE A

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Par F. G. I. JENNEKENS et C. W. M. van VEELEN

(Utrecht)

La vitamine A administrée en fortes doses est susceptible de provoquer des phénomènes d'intoxication. Entre diverses indications, elle est donnée au nourrisson en prévention d'une carence et utilisée en grandes quantités, depuis quinze ans environ, chez l'adolescent et chez l'adulte pour le traitement d'un certain nombre d'affections dermatologiques caractérisées par une hyperkératose. Des raisons d'ordre purement clinique sont à l'origine de cet usage. La carence de la vitamine A entraînant, entre autres symptômes, une hyperkératose de la peau, on a supposé qu'un excès de vitamine A serait susceptible de freiner la kératinisation. A part quelques remarques critiques, on trouve aussi dans la littérature des communications résultant de recherches expérimentales (1) et de données cliniques (2) venant étayer cette supposition. Mais il a fallu constater que l'arrêt du traitement à la vitamine A provoquait une récidive de l'affection cutanée. La voie s'est donc ouverte à l'administration prolongée de la vitamine en forte doses et sans contrôle médical suffisant. Depuis que le phénomène d'intoxication à la vitamine A est mieux connu, il semble, si l'on en croit les communications des dermatologues, que des symptômes plus ou moins graves d'intoxication surviennent beaucoup plus souvent qu'on ne le supposait. L'opinion n'est pas encore fixée sur la question de savoir à partir de quelle dose de tels symptômes sont à prévoir. On a même prétendu que les traitements à la vitamine A étaient dans leur ensemble non justifiés.

Nous reviendrons sur cette question à la suite de l'observation de 2 malades souffrant d'une intoxication due à cette vitamine.

INTOXICATION AIGUE

A l'exemple de Rothman et de Knudson (3), on a coutume de distinguer, chez l'enfant et chez l'adulte, l'intoxication aiguë de l'intoxication chronique.

L'intoxication aiguë offre une image relativement simple. Elle a été décrite chez des explorateurs polaires qui avaient absorbé du foie d'ours blanc, lequel contient, comme on sait, des réserves de millions d'unités de vitamine A. Ces explorateurs souffraient de maux de tête, de nausées et de vomissements, conséquence d'une hypertension intracrânienne ainsi que d'une desquamation de la peau. Ces symptômes disparurent après quelques jours (4).

Marie et ses collaborateurs (5) ont décrit des cas d'intoxication aiguë causée chez des enfants de moins d'un an par des doses de 500 000 U. I. Ces enfants présentaient une fontanelle tendue et bombée en raison de l'hypertension intracrânienne et se montraient parfois irritables et grognons. Le liquide céphalo-rachidien était toujours de composition normale. La tension intracrânienne retrouvait sa valeur après quarante-huit heures environ.

INTOXICATION CHRONIQUE

Beaucoup plus compliquée est l'intoxication chronique survenant après un traitement à long terme de vitamine A.

Nous avons pu en observer un exemple caractéristique chez une malade hospitalisée en Novembre 1935. Mlle A., âgée de 21 ans, prenait, initialement sur l'avis d'un dermatologue, 200 000 U. I. de vitamine A en solution aqueuse par jour pour une acné vulgaire. Elle avait commencé ce traitement en 1933. Durant une année et depuis, elle fit un usage irrégulier du médicament. Elle commençait alors à se plaindre de nervosité, de troubles de la concentration et de chute de cheveux. Par la suite, elle prit le médicament quotidiennement. Après deux ans, les règles devinrent irrégulières. Après deux ans et demi survint un prurit. La malade souffrait de temps en temps à cette époque d'une douleur dorsale assez violente dans la région thoraco-lombale. Après trois ans environ éclatèrent des céphalées, des troubles du sommeil, des mictions fréquentes, des saignements de nez et une diplopie pour le traitement de laquelle la malade entra dans notre service.

A l'examen, on trouve une peau et des lèvres sèches et squameuses et des rhagades aux coins de la bouche. Un érythème accompagné de démangeaisons est localisé à la partie supérieure des bras, aux coudes et aux genoux. Ni le foie ni la rate ne sont augmentés de volume.

Les demandes de tirés à part doivent être adressées au Dr Jennekens, Hôpital universitaire, Nieuwe Gracht 84, Utrecht (Pays-Bas).

Il est difficile de répartir tous les cas d'intoxication à la vitamine A entre les formes chroniques et les formes aiguës. L'une des deux malades présentées ici a souffert d'une hypertension intracrânienne, sans autres affections, après un bref usage de fortes doses de vitamines A.

On évitera le risque de phénomènes d'intoxications, du moins chez l'adolescent et chez l'adulte, en ne dépassant pas une dose de 500 000 U. I. par jour en solution aqueuse et pendant deux mois au maximum. Pour un dosage plus élevé ou de plus longue durée, un contrôle médical régulier est nécessaire.

Aucun ganglion lymphatique anormal n'est palpable. Il y a parésie du droit externe à gauche. Le fond d'œil montre une stase papillaire bilatérale. Les radiographies du squelette n'indiquent pas d'anomalies. L'E. E. G. est irrégulier, légèrement et diffusément anormal. La vitesse de sédimentation atteint 25 mm pour la première heure. Les phosphatases alcalines sériques sont légèrement augmentées : 162 u. sol/min/l (pour une valeur normale jusqu'à 135, d'après la méthode de Bessy). La ponction sous-occipitale effectuée quelques semaines après la première examen fournit un liquide céphalo-rachidien clair sous une pression de 13 cm d'eau. La composition du liquide est normale.

Le traitement à la vitamine A est suspendu le 24 Novembre. Quelques semaines plus tard, la plupart des troubles ont disparu. Après un mois, le taux de vitamine A dans le sérum est encore de 700 U. I./100 cm³ (pour une valeur normale de 50 à 150 U. I./100 cm³, d'après la méthode de Carr et Price). Après trois mois et demi, la teneur en vitamine A est tombée à 235 U. I./100 cm³. La vitesse de sédimentation et les phosphatases alcalines sériques sont alors normales.

L'anamnèse et l'évolution de cette affection sont caractéristiques de l'intoxication chronique à la vitamine A telle qu'on la trouve décrite dans la littérature. Un survol de sa symptomatologie témoigne encore de quelles variétés elle fait preuve.

Peau et muqueuses : L'intoxication s'y déclare en premier lieu. Les symptômes sont d'autant plus significatifs que l'intoxication est plus grave. Ces symptômes sont les suivants : lèvres sèches avec hyperkératose en taches sondes et fissures, rhagades aux commissures des lèvres, peau sèche et squameuse, chute de cheveux, éruptions maculopapillaires, pigmentations en chloasma et gingivite.

Symptômes généraux : Apathie, troubles de la concentration, irritabilité, anorexie, perte de poids, troubles de la menstruation.

Squelette : Douleurs osseuses et articulaires spontanées, parfois violentes, douleurs à la pression de la colonne vertébrale et des extrémités. L'examen radiologique ne révèle d'anomalies que

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chez l'enfant. Seuls Cerbon et ses collaborateurs ont décrit une adulte présentant de telles anomalies. Les clichés montraient chez elle des dépôts calcifiés dans les tractures péricapsulaires, dans les tendons et dans les ligaments, une hyperostose à partir du périoste et des signes de décalcification.

Système réticulo-endothélial : augmentation de volume du foie, parfois de la rate et des ganglions lymphatiques, tendance accrue au saignement pour des temps de saignement, de coagulation et de prothrombine normaux.

Symptômes neurologiques : hypertension intracrânienne, probablement par suite d'une production accrue de liquide céphalo-rachidien (6), provoquant des maux de tête, des nausées et des vomissements, de la diplopie, une impression de vision floue et une stase papillaire. La composition du liquide céphalo-rachidien reste toujours normale.

Certains autres troubles n'apparaissent pas aussi régulièrement, mais n'en sont pas moins les conséquences indéniables de l'hypervitaminose A : exophtalmie, polydipsie, polyurie, incontinence ou parfois rétention des urines.

Signalons dans les résultats des examens de laboratoire une vitesse de sédimentation souvent accélérée. L'augmentation des phosphatases alcalines sériques et un trouble du test de rétention à la BSP n'apparaissent que rarement. Le taux sanguin de vitamine A est toujours augmenté. La réaction à la suppression du médicament est curieuse : le taux sanguin de la vitamine commence par baisser rapidement pour rester ensuite légèrement surélevé durant des semaines ou des mois.

La disparition rapide des troubles subjectifs et de la plupart des troubles objectifs après la suppression du médicament est également très caractéristique. La guérison est complète, et pour autant qu'on le sache, il n'y a jamais eu de cas mortel.

L'image de l'intoxication chronique chez l'enfant diffère en certains points de celle que l'on rencontre chez l'adolescent et chez l'adulte. Cette différence tient surtout au fait que les squelettes en croissance est beaucoup plus sensible à l'hypervitaminose A.

Les lésions sont en général bien visibles à la radiographie : hyperostose à partir du périoste, principalement au niveau de la diaphyse des os longs. Les anomalies se localisent au tibia, au péroné, à la clavicule et aux métatarses. Les parties molles environnantes présentent souvent une enflure douloureuse. Il est probable que l'hyperostose se développe au niveau de la métaphyse et non de la diaphyse seulement avant l'âge de 6 mois. Les os longs s'épaississent alors en forme de pagode (7), principalement à la hauteur des chevilles et des poignets. Une hyperostose du crâne n'a été décrite que rarement et seulement sur l'os occipital et sur l'os temporal (8). Une décalcification du crâne est par contre beaucoup plus souvent signalée. Chez le nourrisson, cette décalcification peut être à l'origine d'un craniotabes. Les phosphatases alcalines sont parfois trop élevées, probablement à la suite de l'affection osseuse. Après l'arrêt du traitement à la vitamine, l'hyperostose disparaît complètement chez l'adulte, alors qu'elle peut laisser des lésions permanentes chez l'enfant. Pease a décrit en effet les cas de quelques enfants avec une anamnèse d'intoxication à la vitamine A. Ils présentaient des troubles de la croissance des grands os longs à la suite d'une soudure prématurée des disques épiphysaires. Ce sont là les seules communications faites à ce sujet jusqu'à présent.

Formes intermédiaires entre l'intoxication aiguë et l'intoxication chronique.

Tous les cas d'intoxication ne peuvent être répartis entre la forme aiguë et la forme chronique. L'exemple nous en est fourni par le cas de notre deuxième malade.

Mme B..., âgée de 10 ans, était en parfaite santé jusqu'en Septembre 1965, hormis une acné vulgaire peu grave. Un dermatologue lui prescrivit pour le traitement de cette affection 300 000 U. I. par jour de vitamine A en solution aqueuse. La malade commença le traitement le 24 Septembre 1965. Trois semaines plus tard apparurent des maux de tête, sensibles surtout le matin et disparaissant au cours de la journée. Les céphalées augmentèrent ensuite pour devenir, après six semaines, si violentes qu'elles s'accompagnaient de nausées et parfois de vomissements. Après sept semaines, la malade est hospitalisée dans notre service et gardée au repos complet. Les maux de tête diminuent alors sensiblement. La malade continue entre-temps à prendre sa dose journalière de vitamine A. Quand nous l'examinons après huit semaines, elle ne souffre plus que d'une impression de vision floue. A l'examen, nous trouvons une légère suffusion. Le fond d'œil révèle un œdème papillaire bilatéral de 4 dioptries et quelques hémorragies péripapillaires. A part une acné vulgaire et une légère adiposité, nous ne trouvons aucune autre affection. Le liquide céphalo-rachidien recueilli par ponction sous-occipitale indique une pression de 30 cm d'eau ; il est de composition normale. La vitesse de sédimentation, quelque peu accélérée, atteint 25 mm durant la première heure. Un jour après l'arrêt du médicament, le taux de vitamine A dans le sang est de 200 U. I./cm³.

Trois jours après l'arrêt du médicament, la vision a retrouvé son état normal. Après une semaine, l'œdème papillaire a sensiblement diminué. Après un mois environ, la tension intracrânienne est normale et l'œdème papillaire a presque disparu.

Germenraad a fait remarquer que la valeur du taux de vitamine A dans le sérum peut baisser sensiblement après quelques jours de conservation du sang (10). Or, le sang de la malade n'a été examiné que trois jours après le prélèvement. On remarquera en consultant le tableau I l'absence de la forte chute initiale du taux sanguin. Il est probable que ce taux était, directement après la suppression de la vitamine, supérieur aux 200 U. I. données par la première analyse.

L'image que présente cette malade est différente de celle que l'on rencontre ordinairement en cas d'intoxication chronique. Tous les troubles proviennent d'une seule affection : l'hypertension intracrânienne. Il y a contraste net avec la variété des symptômes de l'intoxication chronique. La courte pause séparant le début de l'administration de la vitamine et le premier symptôme d'hypertension intracrânienne est frappante. L'observation de cette malade rappelle les cas d'intoxication aiguë tels que Marie et See les ont décrits chez de jeunes enfants. Une réaction indubitable à une brève administration de vitamine A caractérisée par la seule hypertension intracrânienne n'était jusqu'à maintenant pas connue chez l'adulte. Laplane et ses collaborateurs ont décrit le cas d'un jeune homme de 16 ans qui, après avoir pris deux fois 50 000 U. I. de vitamine A à une semaine d'intervalle, présenta des signes d'hypertension intracrânienne accompagnés de convulsions et de symptômes tétaniques (11). Il nous semble improbable cependant que la vitamine A soit ici le seul facteur initial, étant donné surtout la valeur élevée du taux d'albumine dans le liquide céphalo-rachidien.

TABLEAU I. — Quantité de vitamine A par 100 cm³ de sérum exprimée en Unités Internationales.

18 Novembre 1965	200 U. I. par 100 cm³ de sérum.
20 Novembre 1965	215 U. I. par 100 cm³ de sérum.
14 Décembre 1965	210 U. I. par 100 cm³ de sérum.
21 Décembre 1965	155 U. I. par 100 cm³ de sérum.
28 Décembre 1965	135 U. I. par 100 cm³ de sérum.
26 Janvier 1966	115 U. I. par 100 cm³ de sérum.

Marie et See ont été frappés par le fait qu'une partie des enfants examinés ne semblaient pas souffrir de leur fontanelle bombée et de leur hypertension intracrânienne. Notre deuxième malade a présenté également une hypertension intracrânienne durant plusieurs semaines en ne souffrant que d'une impression de vision floue.

Chez la malade d'Oliver, qui montrait une stase papillaire caractérisée, l'importante hypertension crânienne n'avait provoqué qu'une irritabilité accrue (20).

Si la hausse de la tension intracrânienne est susceptible de rester aussi silencieuse, on peut se demander si elle ne survient pas plus souvent qu'on ne le croyait. Cette question est particulièrement importante du moment que chez notre malade, l'hypertension intracrânienne a été provoquée par une dose peu élevée de l'avis des dermatologues. Cette dose était en tous les

cez plus faible que les doses responsables des intoxications aiguës ou des intoxications survenant après un bref usage de la vitamine décrites jusqu'à ce jour. Nous reviendrons encore sur ce point au cours de la discussion.

DISCUSSION

Quelle est la quantité de vitamine A susceptible d'être donnée sans risquer de provoquer des phénomènes d'intoxications ?

Persson, Tunell et d'autres (7) ont décrit les cas d'enfants ne dépassant pas 6 mois et chez lesquels de graves symptômes d'intoxication s'étaient déclarés après une administration de vitamine A à raison de 18 000 U. I. par jour en solution aqueuse. A la suite de ces observations Tunell et ses collaborateurs (12) examinèrent un groupe de 60 nourrissons auxquels ils avaient administré pendant un certain temps 7 500 U. I. par jour en solution aqueuse. Chez un certain nombre de ces enfants, l'examen du sang révéla des taux de vitamine A sensiblement trop élevés. Les auteurs en conclurent qu'il ne faut pas prescrire à des enfants de moins d'une année plus de 2 500 U. I. par jour en solution aqueuse. Cette dose n'en est pas moins supérieure de 1 000 U. I. à celle que le *National Research Council* des Etats-Unis estime suffisante pour prévenir d'éventuelles déficiences.

Pour essayer de répondre à la question de la dose utilisable chez l'adolescent et chez l'adulte, rappelons que la vitamine ne leur est pas prescrite à titre prophylactique, mais en tant que traitement d'une affection. Les dosages, même relatifs, seront donc beaucoup plus élevés. Les quantités prescrites par jour varient de 100 000 à 600 000 U. I. pour un besoin de 2 500 à 5 000 U. I.

Selon des publications dermatologiques comme celles de Frey et Schoch (13), l'augmentation de la dose pour obtenir une action thérapeutique plus prononcée entraine presque toujours des phénomènes d'intoxication. Les publications de ce genre traitent généralement de l'action de la vitamine sur diverses affections cutanées. Elles mentionnent les phénomènes d'intoxication, mais de façon peu détaillée, insistant plutôt sur les complications touchant la peau et les muqueuses. C'est pourquoi, en rassemblant les données déterminant le rapport entre le dosage, la durée de l'administration et l'apparition des premiers symptômes, nous n'avons utilisé que des cas rapportés d'intoxication à la vitamine A (tableau II). On constate à l'examen de ce tableau que les doses ne sont pas supérieures aux doses courantes des traitements dermatologiques. Quelques malades ont même présenté des symptômes graves d'intoxication pour une quantité relativement restreinte de vitamine, soit 40 000 à 50 000 U. I. par jour. La nature de la préparation pharmaceutique de la vitamine est hélas souvent omise dans ces diverses publications. Il est donc difficile de répondre sans plus à la question posée au début de la discussion.

Deux facteurs peuvent contribuer à son éclaircissement :

1. ***Si la quantité de vitamine A administrée est égale ou à peine supérieure au besoin,*** la résorption au niveau du lumen intestinal est à peu près complète (30). Si cette quantité dépasse de beaucoup le besoin, seule une partie en est résorbée. Le pourcentage de la partie résorbée varie toutefois sensiblement suivant les individus. Des troubles de la résorption des graisses peuvent être un facteur défavorable à l'assimilation de la vitamine A. La résorption dépend aussi en grande mesure du mode d'administration. Sous forme de comprimé, la vitamine est moins bien assimilée qu'en solution huileuse. Lewis et ses collaborateurs ont montré en 1947 déjà que, pour une quantité donnée de solution aqueuse, on pouvait obtenir un taux sanguin de vitamine A de trois à cinq fois supérieur au taux obtenu pour une quantité identique de solution huileuse, la perte par les selles étant proportionnellement plus restreinte (31). Une forte dose de vitamine mal résorbée provoquera donc moins rapidement des phénomènes d'intoxication qu'une dose plus faible mais bien résorbée.

Revenant à la dose utilisée par notre deuxième malade, nous pouvons dire que 300 000 U. I. par jour n'est pas, du point de vue dermatologique, une quantité particulièrement élevée. Mais elle le devient si nous considérons qu'il s'agit d'une solution aqueuse.

2. ***Il est probable que la durée de la médication joue également un rôle important.*** La malade décrite par Berger et Roels n'aurait certainement pas présenté de signes d'intoxication si la dose quotidienne assez restreinte de 400 000 U. I. n'avait pas été prise durant de nombreuses années (29). Par contre, de très fortes doses administrées sous forme d'une solution bien assimilable sont en mesure de provoquer après quelques jours déjà les symptômes de l'intoxication dite chronique. L'expérience de Hillman en est un bel exemple (32).

Nous devons donc respecter une grande marge de sécurité dans la détermination d'une dose n'entraînant pas de risques d'intoxication. Oliver n'agit pas autrement en conseillant de prescrire une dose de 50 000 U. I. par jour au maximum et pendant une période ne dépassant pas deux mois. Mais les dosages dermatologiques courants sont bien supérieurs à cette quantité. S'en tenir à la proposition d'Oliver revient à limiter l'usage de la vitamine A à la lutte contre les carences ou à leur prophylaxie.

On a tenté de résoudre cette question de la dose de sécurité en cherchant un rapport entre le taux sanguin de vitamine A et

TABLEAU II. — Quelques données provenant de cas d'intoxication à la vitamine A chez l'adolescent et chez l'adulte, tels qu'ils sont rapportés jusqu'à ce jour. Les cas sont classés d'après l'importance des doses.

Auteurs	Age en années	Sexe	Forme d'administration	Dose	Durée	Premiers symptômes après	Taux de vitamine A dans le sang
Salzberger (14)	44	F	Capsules.	600 000 U. I.	1 an et 6 mois.	1 an.	60 bleu unité.
Cerbey (15)	24	F		500 000 U. I.	5 ans et 6 mois.	1 an et 6 mois.	6 600 U. I.
Rancheu-Nielsen (16)	16	F	Arovit.	300 000 U. I.	1 an.	8 mois.	735 U. I.
Smith (17)	17	M	Gouttes.	300 000 U. I.	5 mois.	5 mois.	
Wiese-Smit (18)	24	F		300 000 U. I.	4 ans.	2 ans.	423 U. I.
Shaw (19)	25	M	Capsules.	300 000 U. I.	8 mois.	6 semaines.	610 U. I.
Oliver (20)	14	F		200 000 U. I.	10 mois.	8 mois.	707 U. I.
Cook (21)	29	M	Aqua sol. A.	200 000 U. I.	2 ans et 4 mois.	2 ans et 4 mois.	
Cook (21)	31	M		200 000 U. I.	6 ans.	Courte période.	
Monro (22)	14	F		200 000 U. I.	10 mois.	8 mois.	620 U. I.
Monro (22)	15	F		200 000 U. I.			
Tutz (23)	17	M		200 000 U. I.	1 an et 6 mois.		
Elliot (24)	21	F	Capsules.	160 000 à 180 000 U. I.	7 mois.	5 mois.	2 773 U. I.
Soto-Bochare (25)	29	F	Comprimés.	150 000 U. I. (1954-1962) 375 000 U. I. (Juillet-Décembre)	6 ans et 5 mois 1/2	6 ans et 6 mois.	2 884 U. I.
Cook (21)	18	F	Aqua sol. A.	150 000 U. I.	8 ans et 8 mois.	1 an.	
Wiese-Smit (18)	20	F		150 000 U. I.	1 an et 6 mois.	1 an.	
Bluke (26)	16	F		100 000 U. I.	4 ans.	3 ans et 8 mois.	250 U. I.
Schwan (27)	28	F		100 000 U. I.	5 ans.		
Monro (22)	16	F		80 000 U. I.	4 ans.		
Black (28)	54	M		50 000 U. I.	3 ans.		
Berger (29)	68	F		40 000 U. I.	8 ans.	Après un certain nombre d'années.	544 U. I.

les symptômes d'intoxication. Mais l'expérience montre que les phénomènes d'intoxication peuvent être minimes ou absents pour un taux sanguin élevé et inversement survenir pour un taux sanguin relativement bas (33). La malade de Stimson, qui présentait pourtant l'image indubitable d'une intoxication chronique à la vitamine A, avait un taux sanguin de 250 U. I. Le sujet examiné par Hillman au cours de son expérience présentait des symptômes caractéristiques avant que le taux sanguin n'ait atteint 300 U. I. La littérature pédiatrique rapporte également des observations de ce genre.

L'absence d'une corrélation directe entre le taux sanguin et l'intoxication peut sans doute être expliquée en partie par le fait que la substance active n'est probablement pas la vitamine A elle-même, mais un de ces métabolites. Cette affirmation est appuyée par l'observation suivante : si l'on donne à un groupe de rats une nourriture déficiente en vitamine A, les symptômes de carence n'apparaissent pas encore au moment où, biochimiquement, la vitamine a disparu de l'organisme, mais survivement après un important laps de temps. On suppose qu'ils ne se déclarent qu'au moment où le métabolite actif a été entièrement utilisé (34, 35).

CONCLUSIONS

Voici les quelques conclusions que nous voulons tirer de ce qui précède :

1° La transition entre l'intoxication aiguë et l'intoxication chronique se fait de manière continue. Les symptômes des formes transitoires dépendent du dosage et de la réabsorption. Certains malades ne présentent, après un usage de courte durée de la vitamine, qu'une hausse de la tension intracrânienne.

2° Il n'y a pas de différences essentielles entre les formes de l'intoxication chez l'adulte et chez l'enfant, hormis l'éventualité de troubles localisés de la croissance, conséquence d'une jonction prématurée des disques épiphysaires.

3° Il n'y a pas de rapport direct entre la valeur du taux sanguin de vitamine A et l'image clinique de l'intoxication. Mais en cas d'intoxication, le taux sanguin est toujours supérieur à la valeur normale.

4° On peut certainement prévoir de graves symptômes d'intoxication après l'administration des doses nécessaires à une action positive sur des affections dermatologiques caractérisées par une hyperkératose. La proportion d'Oliver consistant à ne pas dépasser chez l'adulte une dose de 50 000 U. I. par jour durant deux mois revient en fait à remonter au mode de traitement par la vitamine A, en usage jusqu'à aujourd'hui, des affections dermatologiques caractérisées par une hyperkératose. Cette remarque est également valable pour l'administration de solutions aqueuses.

A notre avis, des doses plus élevées ne sont pas strictement contre-indiquées, compte tenu du caractère réversible des complications éventuelles. Mais un contrôle médical régulier est désirable et le malade doit être averti de l'apparition possible de symptômes d'intoxication.

SUMMARY

Hypervitaminosis A,
by *F. G. I. Jennekens* and *C. W. M. van Veelen* (Utrecht).

It is difficult to distinguish all the cases of vitamin A intoxication between the chronic and acute clinical forms. One of the two patients object of the present work suffered from an intracranial hypertension in the absence of any other sign, consecutively to a short use of high doses of vitamin A.

The risk of intoxication phenomena will be avoided, at least for what concerns the adolescent and adult patients, by not exceeding a daily dose of 500 000 I. U. in aqueous solution during a maximal period of two months. In the case of higher dosage or longer treatment, it is necessary to submit the patient to regular medical check-up.

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Chronic Hypervitaminosis A in an Adult

Robert J. Di Benedetto, MD

Fatigue, musculoskeletal symptoms, skin changes, anorexia, weight loss, and hepatomegaly are the major manifestations of chronic hypervitaminosis A. Withdrawal of vitamin A results in complete recovery. This case is added to the 11 others previously documented in an attempt to stress the importance of earlier diagnosis and increased awareness.

HYPERVITAMINOSIS A has a characteristic picture. Despite this, apparently only 11 cases have been reported in adults.[1-11] In view of the easy access of vitamin preparations and the often injudicious use of these drugs by the public, emphasis is placed on the importance of earlier diagnosis and increased clinical awareness of hypervitaminosis A.

Report of a Case

A 51-year-old white housewife entered the Psychiatric Division of St. Vincent's Hospital on May 13, 1966, complaining of severe depression. In 1961, she had been hospitalized at this institution with a diagnosis of chronic undifferentiated schizophrenia. Since that time, the patient had had repeated hospitalizations for psychiatric difficulties.

In 1945, the patient had maxillary sinusitis. Shortly thereafter, she started taking multivitamins and individual doses of vitamin A for this condition. Vitamin A ingestion was sporadic until 1960. At this time, she began to ingest daily quantities of this vitamin and eventually progressed to a total dose of 600,000 units/day over the three years preceding admission.

In July 1965, she noted the onset of fatigue, diffuse myalgias, and intermittent severe pain in her knees, hips, and shoulders. These symptoms were followed by pain in her legs on walking. Several months later, weakness and generalized loss of body and scalp hair developed. The patient had had bilateral varicosities of the lower extremities with mild ankle edema for many years. However, she noted a marked increase in this edema which did not respond to her usual therapeutic measures. In February 1966, a generalized pruritic, dry, scaly eruption of the skin developed. She was seen at another hospital and placed on a regimen of cutaneous corticosteroid therapy with good results. However, continuous administration of this medication was necessary to prevent recurrence. One month later, loss of her eyebrows and the development of brittle nails ensued.

Physical examination revealed a well-developed, thin, white woman in no acute distress. The vital signs were within normal limits. She was markedly depressed but alert and oriented. The skin was coarse with prominent hair follicles and had a yellowish hue. Examination of the head revealed sparse, coarse hair, particularly over the frontotemporal areas. A generalized loss of body hair was present. Marked thinning of the eyebrows and eyelashes was apparent (Figure). Fundoscopic examination disclosed a right amblyopia which had been present since childhood. A firm, smooth, nontender liver was palpable 6 cm below the right costal margin. The spleen was not palpable. Moderate pressure over both tibias, the shoulders and ankles elicited pain. Bilateral varicosities and 3+ ankle edema were present over the lower extremities. Results of the remainder of the examination were negative.

Sparse coarse hair over frontotemporal area and thinning of eyebrows and eyelashes.

The hematocrit reading was 41%. The white blood cell count and differential were normal. The erythrocyte sedimentation rate was 34 mm/hr (Wintrobe). Results of urinalysis and fasting blood sugar, serum electrolyte, blood urea nitrogen, and uric acid levels were normal. A latex fixation preparation was negative. Cephalin flocculation, serum bilirubin, serum glutamic oxaloacetic and pyruvic transaminases, and lactic acid dehydrogenase values were normal. The alkaline phosphatase level was 5.2 Bodansky units/100 ml. Serum calcium and phosphorous levels were normal. The protein-bound iodine level was 5.7 μg/100 ml. Serum cholesterol value was 177 mg/100 ml. The total serum protein level was 6.5 gm/100 ml, with an albumin level of 3.5 gm/100 ml. Twenty-four hour urinary excretion of follicle-stimulating hormone, 17-hydroxycorticosteroids, and 17-ketosteroids was normal. Serum ascorbic acid value was 0.3 mg/100 ml.

Fasting serum vitamin A level on the 19th hospital day was 440 μg/100 ml (normal 30 μg-70 μg/100 ml), and the serum carotene level was 95 μg/100 ml (normal 100 μg-250 μg/100 ml). Serum vitamin A level 20 days later was 220 μg/100 ml. The alkaline phosphatase and ascorbic acid values at this time were 4.5 Bodansky units/100 ml and 0.15 mg/100 ml, respectively.

Roentgenograms of the chest and bones were unremarkable. An electrocardiogram and an electroencephalogram revealed no abnormalities.

The patient was placed on a regular house diet (5,000 units of vitamin A per day) with no vitamin supplementation. During the first week of hospitalization, the fatigue, myalgias, and pains in her extremities diminished markedly. Her skin gradually returned to its normal color and texture. Six weeks after admission, the liver was no longer palpable, and the ankle edema had decreased. She

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thereafter, early hair growth was noted over her scalp and eyebrows. Her depression gradually improved, and she was discharged nine weeks after admission.

Comment

Two forms of vitamin A intoxication have been described by Knudson and Rothman.[1] The acute type is due to the ingestion of a single large dose and is self-limited with a spontaneous recovery. This particular form was known to polar explorers as long ago as 1857. They noted nausea, vomiting, headaches, and vertigo after eating polar bear liver.[1] The chronic form results from the daily ingestion of moderately toxic quantities over a considerable period of time. All reported cases of adults with hypervitaminosis A have been of the chronic variety.[1-6]

The manifestations of chronic hypervitaminosis A begin insidiously. Although the onset is variable, excessive vitamin intake must persist for at least 8 to 12 months.[1] Stimson feels that a minimum ingestion of 50,000 units of vitamin A per day for 18 months is required.[1] However, Shaw and Nicolli described an individual with findings after six weeks.[3] It is apparent that the ingestion of larger doses will result in earlier manifestations of the disease. This patient took 600,000 units per day for at least two years prior to the onset of symptoms. Hillman induced symptoms of intoxication on two occasions, using doses of 1 million units of vitamin A daily for 14 and 25 days.[4]

Review of all previously reported cases in adults reveals that fatigue, myalgias, anorexia, and weight loss are the most common nonspecific symptoms of this disorder.[1-6]

Arthralgias and bone tenderness are common. In children, these symptoms are always accompanied by bony changes. Periosteal swelling, hyperostoses, and premature closure of the epiphyses may occur.[1,2] Calcification with or without true bone formation in the pericapsular, ligamentous, and tendinous tissues of the joints has been described.[6] Although in all previously reported cases in adults, the patients have had arthralgias, changes have been noted roentgenographically in only one instance.[6] Increased urinary excretion of calcium with normal serum phosphorous and calcium levels has been described.[6]

Among the cutaneous manifestations of hypervitaminosis A are coarse hair, pruritus, dry skin, alopecia, seborrhea, and loss of body hair and eyebrows. This patient evidenced many of these manifestations. Severe gingivitis secondary to excessive intake of vitamin A has also been noted in adults.[1]

Neurological symptoms include headache, diplopia, nystagmus, and convergent strabismus. Signs of central nervous system derangements are much more common in children. Acute hydrocephalus and papilledema have been noted.[1,2] These manifestations have been attributed to the presence of increased intracranial pressure.[1,2]

Hepatosplenomegaly and lymph node enlargement have frequently been encountered in adult patients.[1-6] Several investigators feel that the hepatomegaly is due to the deposition of large quantities of vitamin A in the liver.[1] Bifulco believes the liver enlargement is secondary to fat deposition.[6] Routine histological studies of the liver have failed to disclose any abnormalities.[6]

Numerous abnormal laboratory findings have been noted.[1-6] Anemia, hypoprothrombinemia, hypoproteinemia, elevated serum level of alkaline phosphatase, and increased total body lipids are common. Rodahl has demonstrated that animals with experimental hypervitaminosis A have diminished serum ascorbic acid and decreased amounts of this substance in the liver and adrenal glands.[5] Decreased serum ascorbic acid values were present in this patient and in a patient previously encountered in this institution.[6]

When vitamin A intake is discontinued in patients with hypervitaminosis, serum levels of this vitamin initially fall sharply and subsequently slowly taper off for many weeks.[6] The serum vitamin A level in this patient was 440 μg/100 ml approximately three weeks after withdrawal of vitamin A. Several weeks later, elevated levels (220 μg/100 ml) persisted.

Relief of nonspecific and musculoskeletal symptoms occurs within several weeks upon withdrawal of the drug.[1-6] Hepatomegaly and alopecia are frequently the last manifestations to disappear.

Chronic hypervitaminosis A occurs in patients who take large doses of this vitamin for various dermatological and respiratory disorders and in food faddists who include large quantities of vitamins in their dietary programs.[1-6] The long delay in diagnosis following the onset of symptoms, and the severity and rarity of reported cases in adults, indicate a low index of suspicion among physicians. In view of the marked vitamin production and consumption in this country, milder cases must certainly exist and probably are unrecognized. The manifestations of chronic vitamin A intoxication begin insidiously, and patients frequently fail to volunteer information regarding their vitamin intake. Increased awareness of this entity should result in more frequent clinical recognition. Two adult patients with hypervitaminosis A have been encountered on the wards of this hospital in the past three years.

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Clinical Features of Delirium Occurring During Intensive Coronary Care

Patient	Age (yr)	Sex	Symptoms: Onset (hr)	Symptoms: Duration (Days)	Symptoms: Severity	Cardiac Damage
1	37	M	63	3	Moderately severe	Moderately severe
2	40	M	90	2	Severe	Moderately severe
3	50	M	40	6	Moderately severe	Moderate
4	57	M	37	6	Severe	Severe
5	60	M	60	3	Moderate	Moderate
6	70	F	83	4½	Moderately severe	Severe
7	72	F	57	3½	Moderately severe	Moderately severe
8	72	F	43	7	Severe	Mild
9	76	F	96	4	Moderately severe	Moderately severe
10	60	M	60	5	Moderately severe	Moderately severe
11*	67	M	36	6 hr	Mild	Moderately severe
			15	7	Severe	

*This patient had two distinct episodes five days apart and on during the second episode.

Delirium in a Coronary Care Unit

Donald L. Parker, MD, and James R. Hodge, MD

Eleven patients experienced varying degrees of delirium during the treatment of myocardial infarction in a coronary care unit. Sensory monotony and sleep deprivation seem to be of importance in relation to this state. This potentially serious complication may be combated by placement of the patient in a reassuring and less monotonous environment, and by the judicious use of phenothiazine drugs for sedation.

ELEVEN PATIENTS had delirium during treatment for acute myocardial infarction in a coronary care unit. The basic management of all patients in this unit was complete bed rest, air-conditioned oxygen tent, electrocardiographic monitoring with electrodes and cables attached to both arms and one leg, frequent determinations of pulse and blood pressure, and mild sedation. The care unit consisted of a 12-bed open ward with sliding curtains encircling each bed, overhead lighting, and translucent glass in most windows. Family members of patients were restricted to five-minute visits each hour.

Clinical Observations

Several features of the 12 episodes of delirium in these 11 patients are summarized in the Table. The severity of the symptoms was graded as follows: *mild*, showing brief periods of disorientation or inappropriate behavior; *moderate*, with prolonged confusion and apprehension or restlessness; *moderately severe*, progressing to illusions and imagery (hallucinations) and paranoid ideation; and *severe*, exhibiting combativeness and panic. The extent of myocardial damage was estimated by the degree and duration of elevation of serum glutamic oxaloacetic transaminase level, and the occurrence of hypotension, cardiac failure, or other complications. No apparent relationship existed between the extent of myocardial damage and the severity of the delirium.

The mean time interval from admission to onset of symptoms was 2.3 days with a range of 15 to 96 hours. Disorientation, usually at night, and inappropriate remarks or behavior were often the first manifestations. These were frequently associated with lethargy. Longer periods of confusion, restlessness, and apprehension then developed. Soiling of the bed with urine and stool was a notable feature in several instances. Some patients had illusions of objects or people in the reflections on the oxygen tents; and others experienced hallucinations, talking to imaginary people, and picking at objects in the air. Those who were more severely affected became suspicious, agitated, and combative. Many took off their ECG cables and pulled at the oxygen tents, or tried to climb over the side rails of their beds.

The mean duration of symptoms was 4.5 days. There was a tendency for the less severe episodes to be of shorter duration. During the last hours of their symptoms, the patients usually had long periods of deep sleep from which they often awoke more rational and cooperative. One fatal termination occurred in these 11 delirious patients.

Treatment of the delirium usually consisted of sedation with phenothiazine drugs and the use of soft cloth restraints. However, the patients who responded best were those who had been moved to a side room or transferred to a general medical floor. Their oxygen tents and monitors were removed and family members were allowed to stay with them for long periods, in an attempt to help the patients' reestablish contact with their environment.

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Chronic Vitamin A Intoxication in Adults

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Hepatic, Neurologic and Dermatologic Complications

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Two cases of chronic vitamin A intoxication in adults are described, and the literature is reviewed. Hepatocellular damage, portal fibrosis and eventual cirrhosis may result from chronic vitamin A intoxication in man. Neurologic complications are frequent and consist predominantly of increased intracranial pressure, muscle stiffness aggravated by exercise, and mental changes. Teratogenic effects have been documented in animal experiments and affect primarily the development of the central nervous system. Large doses of vitamin A, if prescribed at all for dermatologic conditions, should be given only for limited periods under close medical supervision and should not be given during pregnancy.

Vitamin A intoxication is a well recognized clinical entity. The acute form is self-limited and rarely presents a diagnostic problem. The chronic form has been observed predominantly in children, but an increasing number of cases have been described in adults. We report two cases of chronic vitamin A intoxication because of some findings hitherto undescribed.

CASE REPORTS

Case 1. An eighteen year old white woman presented in November 1967 complaining of tiredness, dry and cracking skin, soreness and stiffness of muscles after exercise, and infected toe and finger nails. A diagnosis of McArdle's disease had been made elsewhere.

Her illness began in March 1966 as a flu-like syndrome with a skin eruption which was treated with vitamin A (Aquasol A), 300,000 IU daily. She had continued this medication beyond the recommended period of one month, taking 100,000 to 200,000 IU daily because of its favorable effect on her dry skin.

In July 1966 she noticed painful muscular stiffness and fatigue after exercise, more marked in the lower than in the upper extremities, which would subside within half an hour of rest; for example, after riding a bicycle she would be unable to walk because of muscle stiffness in both legs. She also complained of pain in bones and joints, nosebleeds, anorexia, swollen feet, cold forearms and generalized pruritus which was followed within two days by scaling. Severe generalized headache of one week's duration occurred in August 1966. A generalized maculoerythematous eruption, scaling and dryness of the skin were noted. A diagnosis of Stevens-Johnson syndrome was considered. Severe infections of ingrown toe and finger nails then occurred and were resistant to medical and surgical therapy. A diagnosis of McArdle's disease was made in

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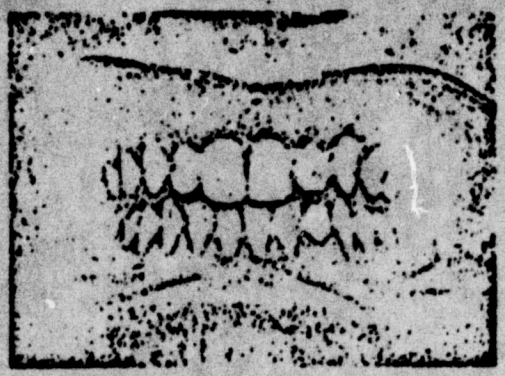

Figure 1. Case 1. Marginal discoloration (bright red) of gingiva.

September 1966. In March 1967 a bright red discoloration of the gingival margin was noted. In summer 1967 the maculoerythematous skin eruption cleared but recurred again for several weeks in the fall. For one year the patient had had an intense craving for carrots and eggs.

The medical and family histories were noncontributory.

Examination in November 1967 disclosed a healthy appearing woman in no distress (temperature 98.7° F, pulse 72/minute, respiration 17/minute, blood pressure 130/90 mm Hg). The skin was dry and scaly. An angular stomatitis and bleeding fissures of the paronychial tissues were noted. Several ingrown toe and finger nails had produced excessive granulation tissue. The gingiva was brightly red at its margin (Figure 1). Café-au-lait spots were noted on the left mid-abdomen and the anterior right thigh. The liver was palpable 4 to 5 cm below the xiphoid in the midline and 3 cm below the right costal margin; it was soft, smooth and not tender. The spleen descended 2 cm with deep inspiration. Neurologic examination showed bilateral subacute papilledema with less than 1 diopter elevation of the disk margins, confirmed by fluorescein studies. The myotatic reflexes were symmetrically increased to a moderate degree, but no pathologic reflexes could be elicited. The remainder of the examination disclosed no abnormalities.

Laboratory data included hemoglobin 11.3 gm/100 ml, leukocytes 4,100/cu mm, erythrocyte sedimentation rate 64 mm in one hour (Westergren), alkaline phosphatase 129 International Units/L, serum glutamic oxalacetic transaminase (SGOT) 80 units/L, sulfobromophthalein retention 32 per cent after one hour, urinalysis grade 1 protein, grade 1 white blood cell count, serum vitamin A 737 μg/100 ml (normal 37 to 45 μg/100 ml), serum carotene 88 μg/100 ml, cholesterol 178 mg/100 ml, cholesterol esters 127 mg/100 ml, phospholipids 173 mg/100 ml, fatty acids 355 mg/100 ml, triglycerides 64 mg/100 ml. Other laboratory tests giving normal results were differential leukocyte count; blood sugar; serum bilirubin, sodium, calcium, phosphorus and creatinine; protein-bound iodine, creatinine phosphokinase; glucose tolerance test; serologic test for syphilis (VDRL); urine screening test for inborn errors of metabolism; twenty-four hour urinary creatinine; electroencephalogram; echoencephalogram; electromyogram; ischemic exercise tolerance test. Roentgenograms of the head showed increased diploic vascular channels in the right frontal area and calcification of the choroid plexus. Roentgenograms of the thorax, lumbar and thoracic spinal regions, feet, right hand and both legs did not disclose any abnormalities.

A bone biopsy specimen was taken from the left ninth rib; the results have been reported elsewhere [1].

The diagnosis of chronic vitamin A intoxication was made, and all intake of supplementary vitamin A was discontinued.

When seen again in January 1968, the patient had recovered from all symptoms. The subacute papilledema was unchanged. Spleen and liver were unchanged in size. Ingrown nails continued to be inflamed, infected and resistant to therapy. Laboratory data were hemoglobin 10.8 gm/100 ml, red blood cell count 3.44×10^6/cu mm, sedimentation rate 87 mm in one hour, alkaline phosphatase 105 units/L, SGOT 55 units/L, prothrombin time twenty-nine seconds; bromsulfalein retention 24 per cent, serum total protein 7.2 gm/100 ml, albumin 3.3 gm/100 ml, serum iron 48 μg/100 ml, serum vitamin A 155 μg/100 ml, serum carotene 351 μg/100 ml. Vitamin K (Synkamin®), 4 mg daily, was prescribed.

In March 1968 the patient still felt well. The liver was palpable 4.5 cm below the xiphoid and the spleen, 2 cm with inspiration. One spider nevus was noted on the dorsum of the right wrist. The subacute papilledema was unchanged. The intraocular pressure was 12 mm in each eye as measured by applanation. Laboratory data included hemoglobin 11.0 gm/100 ml, sedimentation rate 80 mm in one hour, alkaline phosphatase 117 units/L, SGOT 49 units/L, prothrombin time 25 seconds, thymol turbidity 3 units, cephalin flocculation 4+, bromsulfalein retention 34 per cent, total serum protein 7.58 gm/100 ml, albumin 3.42 gm/100 ml, serum vitamin A 119.7 μg/100 ml. Urinalysis disclosed protein 1+, white blood cells 1+, red blood cells 1+. Treatment with vitamin K was continued. The patient was instructed to adhere to a low vitamin A diet with high protein and low fat content.

In July 1968 the optic disks were normal. The liver was palpable 6 cm below the xiphoid and the right costal margin, and the spleen, 3 cm below the costal margin with inspiration. Several spider nevi were noted. The gingival discoloration was barely visible.

Paronychia and infected toenails had healed. Laboratory data included sedimentation rate 82 mm in one hour, alkaline phosphatase 129 units/L, SGOT 53 units/L, prothrombin time twenty-nine seconds, bromsulfalein retention 32 per cent, serum total protein 7.46 gm/100 ml, albumin 3.44 gm/100 ml, serum vitamin A 97.2 μg/100 ml. Urinalysis disclosed protein 1+, white blood cells 1+. In view of persistent signs of active inflammatory liver disease, steroid therapy was recommended, 30 mg of prednisone daily for three weeks followed by 20 mg daily for four weeks and 15 mg daily for one week. However, the patient took only approximately half of the recommended dosage spread over a two month period.

In September 1968, she reported nosebleeds on eight occasions and fatigue. The liver was no longer enlarged; the spleen was palpable 2 cm with inspiration. Four spider nevi were noted on the hands. Laboratory data included a sedimentation rate of 72 mm in one hour, bromsulfalein retention 36 per cent, thymol turbidity 4 units, cephalin flocculation 4+, alkaline phosphatase 94 units/L, bilirubin direct negative, indirect 2.0 mg/100 ml, SGOT 50 units/L, serum total protein 7.65 gm/100 ml, albumin 3.41 gm/100 ml, prothrombin time twenty-one seconds. Needle biopsy of the liver (Figure 2) showed marked periportal and centrilobular fibrosis. Ill defined bands of connective tissue subdivided the lobules and caused distortion of the normal hepatic architecture. There was proliferation of the Kupffer cells and fibroblasts. Small groups of hepatic cells were encased by connective tissue fibers which had formed in the walls of the sinusoids. There was fibrosis of the portal fields. Some of the portal vein branches were markedly dilated. The walls of these veins were thin, and there were no signs of thrombosis. There was some atypical bile duct proliferation. A moderate number of polymorphonuclear leukocytes were found in the areas of intralobular fibrosis. The Prussian blue method (Perl) failed to demonstrate reactive ferric iron. Frozen sections of the specimen showed marked fatty changes with small and large isotropic Sudan IV-positive droplets, predominantly in the hepatic cells and to a lesser degree in the Kupffer cells. The fat showed a marked vitamin A fluorescence, fading from green to blue after about fifteen seconds [2]. The histologic diagnosis was severe hepatic fibrosis and fatty changes of the liver, secondary to vitamin A intoxication.

In March 1969 the patient was feeling well. The liver was palpable 3 cm below the costal margin and the spleen, 3 cm with inspiration. Several spider nevi were uncharged. Laboratory data included hemoglobin 12.6 gm/100 ml, sedimentation rate 85 mm in one hour, bilirubin direct negative, indirect 2.5 mg/100 ml, alkaline phosphatase 71 units/L, SGOT 53 units/L, serum total protein 6.94 gm/100 ml, albumin 3.12 gm/100 ml, bromsulfalein retention 26 per cent, thymol turbidity 4 units, cephalin flocculation 4+, prothrombin time twenty-seven seconds, serum vitamin A 92.1 μg/100 ml, carotene 216 μg/100 ml, cholesterol 454 mg/100 ml, cholesterol esters 295 mg/100 ml, triglycerides 164 mg/100 ml, phospholipids 392 mg/100 ml, total lipids 1,010 mg/100 ml.

Case 2. A 52 year old woman was first seen at the Mayo Clinic in June 1947 complaining of severe gen-

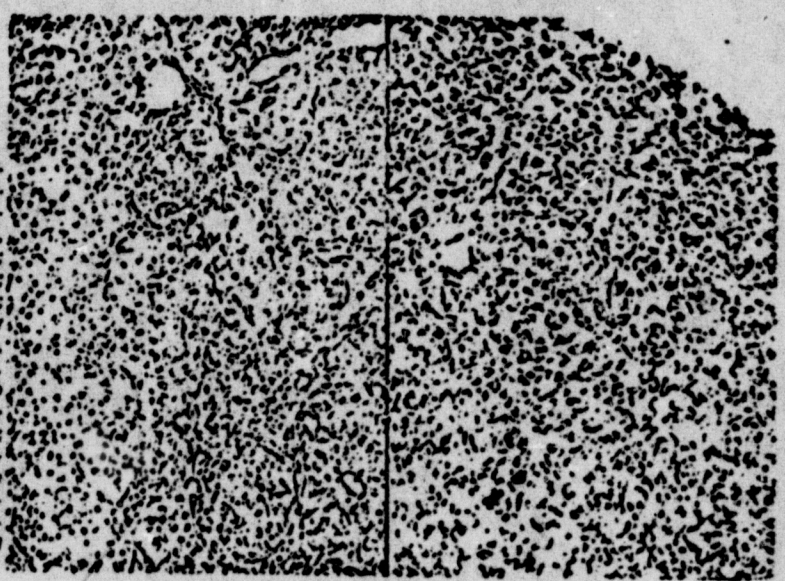

Figure 2. Case 1. Liver biopsy specimen. Left, periportal, intralobular and centrilobular fibrosis; fatty changes, predominantly of hepatic cells; inflammation of portal tracts; proliferation of Kupffer cells; clusters of polymorphonuclear leukocytes. Van Gieson stain, original magnification × 150. Right, hepatic fibrosis with lymphohistiocytic and granulocytic inflammatory infiltrates; small cluster of partly degenerating hepatic cells with fatty changes; loss of normal hepatic architecture. Hematoxylin and eosin stain, original magnification × 165.

eralized pruritus, predominantly of the scalp, shoulders and nuchal area, which had developed in September 1946. The skin had become rough and dry, and she had lost hair. The diagnosis of pityriasis rubra pilaris was made after a skin biopsy. Laboratory data were normal, including sedimentation rate 10 mm in one hour, serum vitamin A 35 μg/100 ml and carotene 131 μg/100 ml. The patient was treated with 3 per cent ichthammol (Ichthyol®) ointment, aluminum subacetate wet dressings, tripelennamine (Pyribenzamine®), and vitamin A (100,000 IU daily); the vitamin A was to be discontinued after three months. She was dismissed to the care of her local dermatologist. Her condition improved approximately 50 per cent. Because symptoms recurred whenever she discontinued vitamin A, she increased the vitamin A intake to 400,000 IU daily for one year and took 200,000 to 300,000 IU/day thereafter for the ensuing eight years.

The family history was noncontributory. The medical history included a hysterectomy in 1945. The patient had never had symptoms of hepatitis nor was there a history of exposure to known hepatotoxins. She had received one blood transfusion in 1950 without complication. In 1949 she had been treated for cystitis with sulfonamides. In 1950 cholecystectomy was performed because of cholelithiasis. In 1952 a deep vein phlebitis healed after conservative therapy. In 1952 she was hospitalized for severe low back pain which subsided with traction. In 1954 she had "low grade arthritis" for which she was treated with phenylbutazone (Butazolidin®) and thyroid preparations.

In September 1954 she experienced pain in the dorsal spinal region. In early summer of 1955, anorexia, nausea and a 16 pound weight loss occurred. At this time the liver was found to be tender and enlarged to the umbilicus. Laboratory data included hemoglobin 11.7 gm/100 ml, red blood cells 3.91 × 10^6/cu mm, bromsulfalein retention 45 per cent after thirty minutes, icteric index 13.9 units, prothrombin time twenty-four seconds, serum total protein 7.6 gm/100 ml, albumin 2.03 gm/100 ml, globulin 5.57 gm/100 ml, sedimentation rate 20 mm in one hour, basal metabolic rate −11 per cent, glucose tolerance test indicative of mild diabetes mellitus. Leukocyte count, urinalysis and plasma cholesterol levels were within normal limits.

An open liver biopsy was performed in October 1955 (in Denver). When the slides were later reviewed at this clinic, the histologic diagnosis was cirrhosis of the liver, probably postnecrotic and cause unknown. No fluorescence studies were carried out. (The paraffin sections were not available for study.) According to the original description by Dr. S. K. Kurland, Denver, the biopsy specimen was firm and gray-yellow; the sectioned surface was lobulated, nodular and varied in color from gray-brown to gray-yellow. Histologically there was marked disorganization of individual lobules with, in many instances, complete loss of the normal central vein and portal triad relationship. The fibrous tissue around the portal triads was increased and contained proliferating bile ducts, focal accumulation of lymphocytes and occasional histiocytes. The histiocytes in many instances were lipoid laden. The fibrous tissue was increased both between portal triads and occasionally between hepatic cell plates. The hepatic cells were finely reticulated. Within some of the liver cells and bile canaliculi was inspissated bile. Regenerative and degenerative changes of hepatic cells were evident in some areas. The diagnosis was cirrhosis, moderately advanced. Subsequent to this biopsy, a high protein, low fat diet was prescribed, and crude liver injections were given intramuscularly twice weekly.

The patient returned to the Mayo Clinic in March 1956, for the first time since 1947, complaining of increasingly severe, nonradiating, midthoracic back pain, anorexia, fatigue, somnolence and yellowish discoloration of the skin.

On examination the vital signs were normal; there was slight generalized icterus, pallor of the face and erythema of the fingers and palms. The liver was palpable at the umbilicus, firm and not tender. The spleen was slightly enlarged. Mild pitting edema of the legs was noted. Neck motions were moderately limited. A mild static and movement tremor of the head, lips, tongue and arms was present. The gait was stiff and slightly unsteady; all muscle groups showed moderately increased tone. The myotatic reflexes were symmetrically hyperactive, but no pathologic reflexes were found. Axillary hair was absent and pubic hair was sparse. The nails were spooned and dystrophic. The remainder of the examination was noncontributory.

Laboratory data included hemoglobin 11.2 gm/100 ml, red blood cells 3.9 × 10^6/cu mm, sedimentation rate 66 mm in one hour, bilirubin direct negative, indirect 1.16, alkaline phosphatase 14.8 Bodansky units, prothrombin time 22 seconds, thymol turbidity 3 units, cephalin flocculation 3+, bromsulfalein retention 26 per cent in one hour, serum total protein 6.66 gm/100 ml, albumin 3.79 gm/100 ml, serum vitamin A 250 μg/100 ml, serum carotene 90 μg/100 ml, cholesterol 234 mg/100 ml, cholesterol esters 167 mg/100 ml, phospholipids 240 mg/100 ml, fatty acids 359 mg/100 ml, total lipids 593 mg/100 ml. A roentgenogram of the thorax showed narrowing of the eighth and ninth thoracic intervertebral spaces.

The diagnosis of chronic vitamin A intoxication was made. Vitamin A intake was discontinued and, within four weeks, the back pain disappeared; the patient's level of energy, alertness and appetite returned to normal, she gained 4 pounds, and there was no abnormality of the skin. She was dismissed on a regimen consisting of a high protein, low fat diet and vitamin K. The vitamin A level four weeks after discontinuation of vitamin A intake was 85.8 μg/100 ml.

On follow-up examination in August 1956 the patient complained of fatigability but otherwise felt well. The scalp hair had become thicker, and the skin was less dry. The liver size was unchanged; the spleen was no longer palpable. One spider nevus was present on the forehead. Laboratory data included hemoglobin 12.1 gm/100 ml, red blood cell count 3.91 × 10^6/cu mm, sedimentation rate 63 mm in one hour, bilirubin direct negative, indirect 1.4 mg/100 ml, prothrombin time twenty-three seconds, thymol turbidity 3 units, cephalin flocculation 3+, bromsulfalein retention 26 per cent, serum total protein 6.5 gm/100 ml, albumin 3.8 gm/100 ml, serum vitamin A 75.0 μg/100 ml, plasma cholesterol 333 mg/100 ml, cholesterol esters 217 mg/100 ml, phospholipids 313 mg/100 ml, fatty acids 527 mg/100 ml, total lipids 860 mg/100 ml.

In September 1957 the patient had no complaints and looked well. The liver was unchanged in size and palpable at the umbilicus; the spleen was not palpable. The myotatic reflexes remained hyperactive. Laboratory data included hemoglobin 13.4 gm/100 ml, sedimentation rate 42 mm in one hour, bilirubin direct negative, indirect 1.34 mg/100 ml, prothrombin time 22 seconds, thymol turbidity 4 units, cephalin flocculation 4+, bromsulfalein retention 36 per cent, serum total protein 6.8 gm/100 ml, albumin 4.1 gm/100 ml, serum vitamin A 31.5 μg/100 ml, serum carotene 181 μg/100 ml, plasma cholesterol 311 mg/100 ml, cholesterol esters 200 mg/100 ml, phospholipids 333 mg/100 ml, fatty acids 507 mg/100 ml, total lipids 818 mg/100 ml.

In December 1961 bromsulfalein retention was 31.3 per cent in one hour cephalin flocculation 4+. In December 1963 bromsulfalein retention was 18.7 per cent in one hour.

In October 1968 the patient felt well and had no complaints. On reexamination by her local physician, the liver was no longer palpable; a roentgenogram of the abdomen showed a normal liver outline. Laboratory data included a hemoglobin of 16.0 gm/100 ml, sedimentation rate 7 mm in one hour, bilirubin direct negative, indirect 1.0 mg/100 ml, alkaline phosphatase 60 units/L, cephalin flocculation 2+, bromsulfalein retention 17.3 per cent after forty-five minutes, serum total protein 6.3 gm/100 ml, albumin 4.03 gm/100 ml, SGOT 38 units/L, cholesterol 257 mg/100 ml.

COMMENTS

The literature contains seventeen case reports of chronic vitamin A intoxication in adolescents or adults, including those reported in this paper [3-15]. They are summarized in Tables I and II.

Sixteen patients were female, and one was male. The age range was fourteen to sixty-two years. The daily vitamin A intake ranged from 41,000 to 600,000 IU, and the duration was two months to nine years. The smallest daily dose leading to intoxication was 41,000 IU taken for eight years [12]. Intoxication after a two-month period of vitamin A intake occurred on a daily dose of 200,000 to 275,000 IU [4].

In the past, vitamin A has been used in large doses over protracted periods for the management of a wide variety of dermatologic conditions, but without adequate therapeutic basis. The reason for vitamin A therapy in the cases reviewed was acne in eight cases, "cold prevention" in two and pityriasis rubra pilaris, nonspecific skin eruption, ichthyosis, food fadism, "to improve vision" and for "dry skin" in one case each.

Our cases confirm the clinical picture characteristic of chronic vitamin A intoxication in adults: the invariably present skin changes, increased intracranial pressure, bone and joint pain, fatigue and anorexia. In addition they exemplify clinical features which have not been emphasized in the past.

Both patients showed marked impairment of liver function, one and a half and twelve years, respectively, after vitamin A intake was discontinued. In

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TABLE I Symptoms and Signs in Seventeen Cases of Chronic Vitamin A Intoxication in Adults and Adolescents

Symptom or Sign	Cases (no.)
Skin (dryness, maculopapular rash, fissures, desquamation, pigmentation, pruritus)	17
Hair loss	14
Generalized weakness and fatigue	14
Pain in bones and joints	13
Marked tenderness of bones to palpation	11
Anorexia	9
Headache	9
Hepatomegaly	8
Muscle stiffness	7
Endocrine (absent or decreased menorrhea)	7
Papilledema	6
Diplopia	6
Weight loss	6
Splenomegaly	6
Polyuria, polydipsia, urinary frequency	6
Psychiatric symptoms	6
Edema of lower extremities	6
Insomnia	5
Bleeding (nose and lips)	5
Brittle nails	4
Somnolence	3
Exophthalmus	2
Yellow discoloration of skin	2
Other neurologic symptoms	2
Gingivitis	1*
Lymphadenopathy	1

*A similar case of gingivitis in vitamin A intoxication has been described by Smith [16] but was not included in this review of seventeen cases.

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TABLE II Laboratory Findings in Seventeen Cases of Chronic Vitamin A Intoxication in Adults and Adolescents

Test	Cases (no.)	
	Normal	Abnormal
Sedimentation rate (mm in one hr)	1	7 (range: 22-87)
Sulfobromophthalein retention (%)	3	3 (17, 26, 32)
Alkaline phosphatase	3	7 (increased)
Serum total protein	8	1 (decreased)
Serum total albumin	1	7 (decreased)
Serum bilirubin: total	7	5 (increased)
direct	7	1 (increased)
indirect	7	1 (increased)
Prothrombin time	4	3 (increased)
Thymol turbidity	9	1 (increased)
Cephalin flocculation	9	2 (increased)
Hemoglobin (gm/100 ml)	8	6 (decreased; range 10.2-12.0)
Leukocyte count (per cu mm)	8	3 (3,200, 4,100, 4,300)
Protein-bound iodine (μg/100 ml)	4	2 (1.8, 10.8)
Cholesterol	6	2 (decreased)
Urinalysis	6	3 (protein 1+)
Cerebrospinal fluid: Pressure (cm water)	3*	3 (35, 60 "increased")
Cells, protein	5	0
Roentgenogram of long bones and spine	11	2 (demineralization)
Electroencephalogram	4	2 (diffuse abnormality, projected type)
Serum vitamin A (μg/100 ml)	0	17 (range, 83-2,000)
Serum carotene (μg/100 ml)	6	3 (slightly increased; range 264-375)

*These normal values were 13/13, and 7 cm water.

Case 2, liver size returned to normal, and liver function improved slowly. Neither patient gave any history of hepatitis or exposure to hepatotoxic substances other than vitamin A. This, the fluorescence microscopic findings in Case 1 and the improvement after discontinuation of vitamin A intake in Case 2 suggest strongly that the impaired liver function and the morphologic changes in hepatic tissue were a result of the hepatotoxic effect of vitamin A. Hepatomegaly has been noted in six other cases of chronic vitamin A intoxication [4,6,7,10,11,15]. A liver biopsy was normal in one case [11]. Hepatic cell necrosis, fatty changes and other pathologic findings in the liver of experimental animals reported by numerous investigators seem to confirm the hepatotoxic effects of excess vitamin A [17]; the cause of death in these animals frequently was widespread hemorrhage due to hypoprothrombinemia secondary to marked loss and impairment of hepatic parenchyma. These experimental findings, however, refer to results of acute intoxication. The biopsy findings in our two cases suggest that, in man, chronic hypervitaminosis A may lead to hepatocellular damage, portal fibrosis and eventual cirrhosis.

A marked increase in plasma lipid levels was noted in both of our cases after discontinuation of vitamin A therapy and may be related to impaired liver function. However, it is of interest that the increase occurred shortly after vitamin A intake was discontinued. Misra [18] reported an increase in total brain lipids and cholesterol in vitamin A intoxication.

The cerebrospinal fluid pressure was measured in six of the cases reported in the literature: it was increased in three [6,8,14] and normal in three [9,12,13]. In the three cases in which pressure was increased, it was associated with papilledema twice, diplopia three times and headache twice. In the three cases in which the pressure was found to be normal, it was measured several weeks after vitamin A therapy was discontinued in one case, was not associated with papilledema or diplopia in the second case, and was measured after pneumoencephalography in the third case. In the case reported by Gerber and associates [6] the cerebrospinal fluid was found to be under increased pressure when ventriculography was performed. A craniotomy was carried out on this patient; she continued to take vitamin A, and the craniotomy site was repeatedly found to be tense and markedly bulging. Jennekens and Van Veelen [13] reported a case of subacute vitamin A intoxication (not included in our review of chronic cases) in a nineteen year old patient with diplopia, papilledema and headache; an elevated cerebrospinal fluid pressure (300 mm water) was found. These findings strongly suggest that chronic vitamin A intoxication in adult man causes increase of cerebrospinal fluid pressure with diplopia, papilledema and headache. This is in contrast to the results of animal experiments

[19,20] but is in accord with the prompt bulging of fontanels observed in acute vitamin A intoxication in infants [21] as well as the observation of increased intracranial pressure and hydrocephalus in offspring of rats fed excessive doses of vitamin A [22].

Only few neurologic signs, other than increased intracranial pressure with associated diplopia, somnolence and headache, have been reported in man. Gerber and co-workers [6] described nystagmus, atrophy of selected muscles and sensory symptoms in the saddle area in their patient.

We would like to call attention to a neurologic symptom which, in one of our patients, led to the mistaken diagnosis of McArdle's disease. It consists of muscle stiffness which may or may not be present spontaneously but will occur or be markedly increased with activity and subside with rest. This symptom can become severe enough to make walking impossible, was observed in seven of the seventeen cases reported in the literature [6-8,11,15] and may lead to bizarre postures. It is not known whether this symptom is of myogenic or neurogenic origin.

Psychiatric manifestations have been prominent in several cases and may lead to social isolation of the patient; in mild cases they presented as depression or irritability.

Numerous central nervous system changes have been reported to occur in vitamin A intoxication of experimental animals, including exencephaly and anencephaly in offspring of vitamin A-intoxicated rats [22], neuronal changes in the neuroepithelial zone in offspring of mice [23], higher incidence of postvaccinal encephalomyelitis in rabbits [24] and widespread neuronal degeneration in guinea pigs [25].

The rather striking gingivitis present in one of our patients has been reported on only one other occasion [16].

Paronychia and infected ingrown toenails associated with abnormal granulation tissue in one of our patients subsided after vitamin A therapy was discontinued and were probably related to the hypervitaminosis.

We have no explanation for the craving for food with high vitamin A content which has been reported by others and was present in one of our patients. It occurs during the state of hypervitaminosis.

Laboratory tests in the reported cases showed variable results except for consistently increased serum vitamin A levels. Other abnormal findings were increased cerebrospinal fluid pressure and abnormal liver function tests. Anemia, leukopenia and proteinuria were present in a few cases. Electroencephalographic abnormalities were reported in two cases in which there was evidence of increased intracranial pressure. Demineralization of bones was detected roentgenologically in only two cases, in contrast to marked bone abnormalities with spontaneous fractures usually noted in acute animal experiments. In one of our cases there were no grossly detectable roentgenologic bone changes, but marked alterations in bone turnover were noted in the biopsy specimen [1].

It is of importance that, in chronic vitamin A intoxication, storage of vitamin A in the liver and serum levels of vitamin A are not proportionally related. During early stages of intoxication much of the vitamin A is stored in the liver, and the serum level remains low. Once the capacity for storage is exhausted, the serum level increases rapidly. For this reason, serum vitamin A levels may be high if a relatively small amount of vitamin A is given for a sufficiently long period. The serum vitamin A level may remain low if large amounts of vitamin A are given for short periods.

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Benign Intracranial Hypertension Associated With Hypervitaminosis A

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MANY explanations have been proposed concerning the etiology of benign intracranial hypertension (BIH).[1-100] The syndrome of chronic headache, papilledema, increased intracranial pressure, and occasional related visual field defects and sixth nerve palsies.[1-10] The patients are alert, and the electroencephalogram is usually normal,[11] as are the cerebrospinal fluid (CSF) protein level and cell count. Pneumoencephalogram shows a small or small ventricular system, and no distortion of extracerebral CSF patterns.[1-7] Brain edema has been noted on biopsy, with thickening of all cellular elements.[12] Papilledema can occasionally be so severe as to constitute a threat to vision.[7] The majority of patients experience a self-limiting course, with rare recurrence.[13]

Implicated as causative factors have been the following: (1) obstruction or impairment of intracranial venous drainage[7,14-20]; (2) endocrine and metabolic dysfunction[19,21-23] including obesity,[20-23] menstrual disorders,[24,25] pregnancy,[24,27] menarche,[28] Addison's disease,[29] and hypoparathyroidism[30-32]; (3) exogenously administered drugs[30,33] including adrenal steroids,[34-36] female sex hormones,[37-41] antibiotics,[42-47] and other therapeutic drugs[37]; and (4) systemic disorders[48-54] including iron deficiency anemia,[55,57] blood dyscrasias,[54,58] allergy,[59] diabetes mellitus,[71] Sydenham's chorea,[72,73] sarcoidosis,[74] trypanosomiasis,[75] infectious mononucleosis,[76] roseola infantum,[77] lupus erythematosus,[78] respiratory insufficiency secondary to chronic lung disease,[79-84] muscular dystrophy,[91] and polio.[92,93] A familial form of BIH has been recently described.[94] Hypertensive encephalopathy[95] and lead intoxication[96] may also present with papilledema. Papilledema with increased intracranial pressure, and without evidence of intracranial mass lesion, may be seen in conditions associated with elevated CSF protein levels such as polyradiculoneuritis[97-101] and spinal cord tumor.[102-108]

In 1954 Gerber et al[109] first reported hypervitaminosis A associated with pseudotumor cerebri in an adult. Since then, only three other cases in young adults have been reported.[110,111]

Report of Cases

CASE 1.—A 20-year-old white man was admitted to Jefferson Medical College Hospital on Oct 11, 1964. Approximately four to five months prior to admission the patient developed mild, steady, dull, nonthrobbing frontal headaches lasting a few hours each, and usually relieved by aspirin. The headaches occurred about once a week, were present often on awakening in the morning, and were somewhat aggravated by coughing and bending over. Two to three weeks prior to admission he noted occasional episodes of blurred vision that lasted a few seconds each, brought on by exertion or by sudden changes from the recumbent to the sitting position. The remainder of the neurologic system review was normal.

The patient had been periodically followed ophthalmologically for minor external eye trau-

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sus, and significantly, fundoscopic examination on April 6, 1964, six months prior to admission, was normal. The general medical history revealed that the patient had been suffering from keratosis follicularis, a chronic skin condition for which vitamin A is a recommended treatment.[12] The diagnosis had been confirmed by biopsy four years prior to his present admission, and he had been treated with high oral doses of vitamin A during this time. The daily oral dosage of vitamin A varied between 100,000 and 500,000 units and was taken continuously for four years (since July 1960). The dosage variability was determined by the clinical situation (Table 1).

General physical examination on admission revealed a thin, muscular, white male patient in no distress, who complained of a mild headache. Vital signs were normal. Significant findings included a diffuse papulovesicular, oily, crusting eruption on the shoulders and face, cracking and dryness of the lips, and tenderness over the lumbar spine. The liver was approximately 2 cm below the right costal margin and very tender to palpation. There was no splenomegaly or palpable lymphadenopathy.

Neurological examination revealed an alert, cooperative, intelligent patient who had no defects of mentation, speech, or memory. The extraocular movements were full without nystagmus or ptosis. Visual field testing revealed enlargement of the blind spot bilaterally, with no scotal defects or scotomata. Visual acuity was 6/6 bilaterally. Funduscopic examination revealed 2 to 3 diopters of papilledema bilaterally. Pupils were round, regular, equal, and reacted briskly to light. The remainder of the examination was completely normal.

Admission laboratory studies revealed that hematocrit, hemoglobin, white blood cell count (WBC), urinalysis, blood urea nitrogen (BUN), fasting blood glucose, protein-bound iodine (PBI), Venereal Disease Research Laboratory (VDRL) test, skull and chest roentgenograms, EEG, and electrocardiogram were all completely within normal limits. Liver function studies revealed normal values for serum glutamic oxaloacetic transaminase (SGOT), lipase, and bilirubin, with abnormal values for alkaline phosphatase (4.9 Bodansky units) and prothrombin time (40%).

Serum vitamin A level, two weeks prior to admission, was elevated (131 μg/100 ml). Serum carotene done simultaneously was normal (31 μg/100 ml). Spinal fluid examination at time of admission revealed an opening pressure of 340 mm of CSF; the fluid was clear and colorless; there were no cells; total protein level was 35 mg/100 ml; colloidal gold curve was

Table 1.—Relationship of Serum Vitamin A Level to Vitamin A Intake (Case 1)

Date	Vitamin A Serum Level (μg/100 ml)	Vitamin A Dosage (units/day)
July 23, 1960 (control)	23	0
July 1960 to January 1961	123-165	500,000
January 1961 to July 1961	94-84	100,000-150,000
December 1961 to June 1962	110	400,000-500,000
July 1962 to December 1962	24-99	100,000-300,000
January 1964 to admission	96-130	500,000

60011111000; and serologic test for syphilis was reactive. Repeat lumbar puncture eight days later revealed an opening pressure of 420 mm of CSF; the fluid was clear and colorless; the protein level was 42 mg/100 ml; and no cells were seen.

Vitamin A was discontinued at the time of admission. On Oct 21, 1964, the patient had a pneumoencephalogram which was completely normal. During the period of hospitalization his neurological examination, other than for eye findings, remained within normal limits. Following discharge from the hospital, the papilledema and visual field defects returned to normal in six weeks. The patient continued to have gradually decreasing frontal headaches for three months, but since then has been completely asymptomatic from a neurological standpoint.

Case 2.—A 20-year-old white female laboratory technician was admitted to Jefferson Medical College Hospital on Nov 16, 1960, with the chief complaint of double vision, first noted two days prior to admission. General medical history revealed that the patient had been taking 100,000 units of vitamin A daily for acne for approximately 3½ years prior to the onset of symptoms. On Oct 29, 1960, the patient encountered the sudden onset of horizontal diplopia which was accentuated by focusing on distant objects. She denied any symptoms of headache, decreased visual acuity, focal weakness, paresthesias, or other neurological symptoms. Bilateral papilledema was seen in the Eye Clinic at Jefferson Medical College Hospital on Nov 16, 1960.

General medical examination was normal. There was no hepatosplenomegaly, lymphadenopathy, or bone tenderness. Ophthalmologic examination revealed 3 to 4 D of papilledema bilaterally. There were many small hemorrhages about the edge of the elevated disks. The retinal veins were distended and pul

with compression. No other ... or extraocular muscle ... noted. Peripheral visual ... noted enlargement of the ... by. The visual acuity was ... The remainder of the neu... was completely normal.

Laboratory studies ... hemoglobin, WBC, fasting ... liver function studies, ... PBI were within normal ... were normal (0.06 μg/100 ... level was not obtained. An ... grams of the skull, chest ... heads were all normal. ... lumbar puncture examinat...

During her stay in the ... stopped taking all vitami... ...ts of lymphilised urea in ... days. On Nov 24, 1... admission, ophthalmologi... ...ocular lessening of the ... peripheral fields showed ... ...ponching normal.

The patient was discharg... ...ved has had no recurrenc... ...ptic lesions. Vitamin A wa...

Comme...

Two forms of vitamin ... generally recognized, ... Acute vitamin A intoxi... ...generalized as well as ... form (CNS) symptoms ... in 1636 by Elisha Kane[13] ... He recorded symptom... headache that would ... during the ingestion of ... which later was found ... concentration of vitamin ... century later, acute hype... ...ed in adults associ... ...d liver, also rich in ... symptoms were acutely ... frontal headache, na... drowsiness, and irri... Acute intoxication with ... from accidental or ... dosage, documented by ... blood vitamin A levels, ... by Marie and Sée.[14] ... fontanelles, vomit... were present. Cerebrosp... were elevated. Symptoms ... clear after cessation ... ...e hydrocephalus of in...

of Serum Vitamin A Level Intake (Case 1)

tamin A um Level /100 ml)	Vitamin A Dosage (units/day)
23	0
12-166	400,000
14-84	100,000-150,00
110	400,000-500,0
14-66	100,000-300,0
8-120	500,000

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examination. No other funduscopic, pupillary, or extraocular muscle abnormalities were noted. Peripheral visual field examination revealed enlargement of the blind spots bilaterally. The visual acuity was normal bilaterally. The remainder of the neurological examination was completely normal.

Laboratory studies including hematocrit, hemoglobin, WBC, fasting blood glucose, BUN, liver function studies, serum electrolytes, and urinalysis were within normal limits. Serum carotene was normal (0.06 μg/100 ml), but a vitamin A level was not obtained. An ECG and roentgenograms of the skull, chest, and bones of the limbs were all normal. The patient refused lumbar puncture examination.

During her stay in the hospital, the patient continued taking all vitamin A and received 7 cc of hyaluronidase in 10% invert sugar intravenously. On Nov 24, 1960, eight days after admission, ophthalmologic examination revealed lessening of the papilledema and the visual fields showed the blind spots to be approaching normal.

The patient was discharged on Nov. 24, 1960, and had no recurrence of symptoms or signs. Vitamin A was discontinued.

Comment

Two forms of vitamin A intoxication are clinically recognized, acute and chronic. Acute vitamin A intoxication resulting in central as well as central nervous system (CNS) symptoms was first alluded to in 1853 by Elisha Kane[113] the Arctic explorer. He recorded symptoms of vertigo and headache that would transiently occur following the ingestion of polar bear liver, which later was found to contain a high concentration of vitamin A.[114] Nearly one hundred years later, acute hypervitaminosis A was described in adults associated with ingestion of polar bear liver, also rich in vitamin A.[115] The symptoms were acutely manifested by vio- lent frontal headache, nausea, vomiting, vertigo, dizziness, and irritability.

Acute intoxication with vitamin A in children, from accidental overdose of vitamin A, documented by abnormally high serum vitamin A levels, was described in 1947 by Marie and Rivière.[116] Marked bulging of the fontanelles, vomiting, and drowsiness were present. Cerebrospinal fluid pressure was elevated. Symptoms cleared within a few days after cessation of vitamin A. This was hydrocephalus of infancy secondary to hypervitaminosis A could only be duplicated by using natural vitamin A by mouth. Neither orally administered synthetic vitamin A, nor parenterally administered natural vitamin A caused any abnormal effects.

Chronic vitamin A intoxication was first described in a child with general systemic symptoms only.[117] In a later report, Gribetz et al[118] observed a child with enlargement of the head and slight dilatation of the lateral ventricles seen by pneumoencephalogram. These findings were reversed upon reduction of vitamin A.

The first documented case of chronic vitamin A intoxication in adults was reported by Sulzberger and Lazar[119] in which only general systemic symptoms were present.

The initial description of neurological signs and symptoms seen in chronic hypervitaminosis A was presented in 1954 by Gerber et al,[120] who noted the progress of a 21-year-old woman who had been taking high doses of vitamin A for one year when she developed diplopia, headache, nausea, and blurring of vision. On examination, she was noted to have blurred disc margins, retinal hemorrhage on the right disc, and end point nystagmus. While under observation over a period of 7½ years, and continuing her intake of vitamin A, she developed a definite increase in her choked disc, progressing to eventual optic atrophy. Ventriculography revealed very slight dilatation of the lateral ventricles with no shift of position. She was treated by a subtemporal decompression which stopped bulging ten weeks after discontinuance of vitamin A.

In 1958, Oliver and Havener[110] described a 14-year-old girl who had been taking 200,000 units of vitamin A for treatment of acne vulgaris during the ten months prior to admission. She presented with dry skin and joint pain, and had no CNS or visual symptoms. Papilledema was discovered as an incidental finding. Lumbar puncture revealed opening pressure of 600 mm of CSF with normal values for cells, protein, and glucose. Within one month after discontinuation of the vitamin A, the papilledema subsided, and her eyegrounds were noted to be normal at that time.

In 1960, Morrice et al[111] described two additional cases of pseudotumor cerebri in young adults on long-term vitamin A thera-

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Table 2.—Summary of Clinical Data in Six Patients With BIH Secondary to Vitamin A Intoxication

Age	Sex	General Medical Symptoms	Initial Neurological Symptoms	Duration on Vitamin A	Daily Amount Vitamin A	Intoxication	Duration Neurologic Symptoms After Vitamin Discontinu
14-21	F (5) M (1)	Joint pain Dry skin and mucous membranes Skin rash Hair falling out Hepatosplenomegaly	Papilledema (6) Diplopia (4) Blurred vision (1) Headache (3)	10 mo-4 yr	25,000-500,000 units daily	Acne (4) Keratosis follicularis (1)	3 weeks-6 mo

py. The first, a 16-year-old girl, was receiving 50,000 units of vitamin A a day when she developed skin and hair changes. Fundoscopic examination revealed bilateral elevation and blurring of the optic discs. Electroencephalogram and pneumoencephalogram were normal. Her papilledema persisted for several months after cessation of vitamin A ingestion, then gradually cleared. The second patient was a 15-year-old girl who had been taking oral doses of vitamin A ranging from 50,000 to 200,000 units per day. Duration of vitamin A dosage was not noted. She also presented with dry skin and mucous membrane, joint stiffness, somnolence, diplopia, headache, tinnitus, anorexia, and nausea. On examination, she was noted to have bilateral papilledema, splenomegaly, and a thinning of hair texture. Neurological examination was otherwise normal, as were her arteriogram and pneumoencephalogram. The papilledema resolved five months after discontinuation of the vitamin A.

A summary of the clinical data of patients with BIH secondary to hypervitaminosis A is seen in Table 2.

Experimentally, increased maternal vitamin A intake during gestation produces hydrocephalus and exencephaly, along with other congenital anomalies in newborn animals.[120,121] Conversely vitamin A deficient newborn and adult animals also develop an increase in both CSF pressure and volume[122,123] with hydrocephalus present at autopsy.[124,125] Aqueductal stenosis[124] or disturbance in skull bone growth were thought to be possible contributing factors.[125] The severity of this hydrocephalus was related to the degree and length of vitamin A deficiency, and was reversible by vitamin A therapy.[126]

Clinically vitamin A *deficiency* in rabbits has resulted in hydrocephalus which responded promptly to vitamin A.[127-129] Associated neurological findings including rigidity, spasticity, hyperactive reflexes, a bulging anterior fontanelle were also promptly reversed.

Although vitamin A deficiency in adults has been associated with night blindness and perhaps keratosis follicularis,[112] no neurological signs or symptoms, either pseudotumor or others, have so far been reported.

Summary

Two cases have been presented of chronic vitamin A intoxication in young adults, resulting in the syndrome of pseudotumor cerebri or benign intracranial hypertension (BIH). Clinical and experimental observations on the relationship of vitamin A to cerebrospinal fluid (CSF) are reviewed. It is apparent that both vitamin A deficiency and hypervitaminosis A can be associated with a rise in CSF pressure.[130]

Skin, mucous membrane, joint, and musculoendothelial changes in a patient with BIH should alert the clinician to the possibility of vitamin A intoxication.

This investigation was supported in part by grant No. NB 05135-12 from the National Institutes of Health.

Nonproprietary and Trade Names of Drugs

Urea for injection—*Ureaphil, Urevert.*

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Indication		Duration Neurolog. Symptom After Vitam Discontin.
Acne	(4)	3 weeks
Keratosis follicularis	(1)	6 mo

...to vitamin A. ...
...l findings including ...
...hyperactive reflexes, ...
...or fontanello were ...

...in A deficiency in ad...
...ed with night blinds...
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Hypervitaminosis Causing Pseudotumor Cerebri

To the Editor.—A young woman with excess vitamin A intake presented with headache, diplopia, and papilledema which regressed when the taking of the vitamin was stopped. This is an unusual case in an adult, with pseudotumor cerebri as the only manifestation of hypervitaminosis.

Report of a Case.—An 18-year-old female student entered the Ohio State University Hospital on Dec 3, 1969, complaining of double vision and headaches. For the previous three months, she had noted nonspecific generalized headaches. One month prior to admission, she noted the onset of a rubbing noise in her right ear and peripheral visual difficulty. Five days before admission she developed persistent diplopia and papilledema. There were no other symptoms.

Vitamin A tablets, 50,000 units three times a day, had been prescribed four years previously. She had a mild case of acne and was given tetracycline intermittently during this four-years period. She had been taking vitamin A regularly, but no tetracycline in the previous two months.

The pupils were equally reactive to light; the sclera were clear, and both fundi showed 4-diopter papilledema, with a small exudate in the right eye and a small fresh hemorrhage in the left eye. Visual acuity was 20/20 bilaterally, with enlargement of both blind spots. Numerous laboratory and radiological findings were normal. The electroencephalogram showed a delta grade II diffuse pattern, which was consistent with increased intracranial pressure. The serum carotene value was 162 μg/100 ml (normal, 100 μg to 250 μg), and serum vitamin A was 384 international units (normal value for adults 150 to 250). The patient was advised to discontinue taking the vitamin A, and examination six months later revealed no papilledema, a normal blind spot, and a vitamin A level of 35 μg/100 ml (normal, 20 μg to 60 μg/100 ml; by a different method).

Comment.—Elisha Kent Kane in 1857 described "Vertigo, diarrhea, and their concomitants," after a meal of polar bear liver.[1] Frederick Jackson in 1899 described headaches six hours after eating polar bear liver on two different occasions.[2]

In 1942, Rodahl and Moore identified the toxic substance in polar bear liver as vitamin A. When the liver was freed of vitamin A content, no toxic symptoms resulted.[3]

Seven cases of chronic vitamin A intoxication have been documented in adults,[4-10] although frequently reported in children. In none of the cases—adults or children—has papilledema been the only finding.

The smallest dose of vitamin A reported to produce symptoms in an adult is 50,000 units given during an 18-month period. Complete recovery occurs in a few months when administration of vitamin A is stopped. All previous patients described had musculoskeletal symptoms; five patients had hair loss, and hepatomegaly was found in five. Only three of the seven adults had any neurologic findings.

The evidence of pseudotumor cerebri in this case is based on increased intracranial pressure, as manifested by papilledema and diplopia, with a normal brain scan and normal skull roentgenograms. The disappearance of the signs and symptoms, with concurrent reduction of serum vitamin A to a normal level over a period of several months, is given as evidence that vitamin A was the causal agent.

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Edetic Acid Therapy

To the Editor.—The Food and Drug Administration has recently stated that unless further information is made available regarding the efficacy of the oral form of edetate calcium disodium (EDTA) that after six months, this form will be removed from the market.

Recently, during the screening of six workers in a stained glass window factory, three were found to have elevated blood lead levels (> 60 μg/100 ml). Since two of these three patients' blood levels were only slightly elevated (81 μg/100 ml), each was treated with an oral course of edetate trisodium ("Versenate Sodium"), 4 gm daily for five days, with reduction of blood lead levels to normal. (The third case with much higher levels was treated parenterally.)

Because of other experience which would favor the efficacy of oral administration of EDTA by varied criteria, it appears to us that the 6-month period is inappropriately short to obtain sufficient data for documentation of efficacy by the Federal Drug Administration (FDA). This is particularly true because of our current protection against environmental hazards of lead and the relatively restricted experience possible to any single physician or investigator.

It would appear to us to be appropriate for all interested physicians to submit case reports directly to the FDA in objectively documenting their experience with oral administration of edetate calcium disodium. To abruptly remove this drug from the market could have deleterious effects on American public health.

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Uvulazation

The
Lingual
Backlash
Flap in the breeze
From verbal diarrhea
Say ah . . . . .
How palatial!
Tail piece
of
The
Soft Palate
Dam
The
Post
Nasal
Drip.

Ramon Pessens, MD
New York

Acta Dermatovener (Stockholm) 50: 109–113, 1970

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HALIBUT LIVER POISONING IN 11 FISHERMEN

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Abstract. Eleven fishermen developed symptoms of acute vitamin A poisoning 5 hours after eating from 20 to 300 g of fried halibut liver, containing approximately 2–30 million units of vitamin A. The liver came from an unusually large halibut with a length of 2 m, which had been caught in the North Atlantic. The case history of one patient is reported in detail. The most striking symptom was the generalized desquamation of the skin, beginning 24 hours after the meal. Serum vitamin A levels were elevated in all.

Acute vitamin intoxication have been described as early as 1597 (20), but have only been recognized as such since the work of Rodahl & Moore in 1943 (17). Most descriptions were related to the eating of liver of polar mammals and fish by arctic travelers (3, 8, 9, 12, 19).

Recently we had the opportunity to observe a small epidemic of vitamin A intoxication in a group of 11 fishermen who ate fried halibut liver. They developed characteristic skin- and general symptoms and elevated serum vitamin levels. The most severely ill patient could be followed during the whole course of his illness, the others were followed at intervals.

Since such descriptions in the medical literature are relatively rare (1, 10, 13, 15, 16), we would like to record our findings.

Epidemiological data

On January 28, 1969, the trawler "Alida" (Scheveningen 6) was fishing near the Lofoten islands off the Norwegian coast at 70° N latitude. Around 5 p.m. the nets were hauled in. During the "stripping" of the catch, the liver of a very large halibut (length about 2 m) was put into the refrigerator for the crew's supper. It was fried later in large slices in salad oil and served with bread and salt at 7.30 p.m. The first engineer who did not like liver, did not join in the meal.

At 9 p.m. when the nets were hauled in again, everyone felt well. At 1 a.m., however, when the whole crew turned out for work again, all except the first engineer had become ill. The men complained of dull heavy headaches, dizzyness and nausea; 4 men vomited. The next day all men appeared to have redness and desquamation of the skin. All but one sailor felt better. Appetites were normal. When the home port, Scheveningen, was reached several members of the crew visited their family doctors to show their red, peeling skin. All were able to sail again a few days later.

CASE REPORT

One sailor, however, had symptoms severe enough to warrant consultation of a dermatologist. This was on February 6, one week after the ingestion of the fried liver. The sailor was a 23-year-old heavily built man with a weight of 90 kg and a height of 176 cm. He had eaten the largest amount of liver, approximately 300 g. The day after the meal he still felt dizzy. His face had been red and swollen, his arms, legs and chest also had shown erythema. There were no skin changes on the back. His temperature (taken by the skipper) had been normal. Patient had not vomited, there was no diarrhoea and his appetite was good.

Dermatological examination showed slight desquamation of the skin of the nasolabial folds, the presternal area and the medial side of the upper legs. There was no erythema to be observed. The main skin changes were concentrated on the palms of the hands (Fig. 1) and the soles of the feet. The palms were markedly erythematous and edematous; the horny layer was desquamating in thick yellow sheets. In the center of the palms, the skin under the loose layers of keratin contained air. The dorsal sides of the feet and hands showed only slight erythema. A punch biopsy was taken from an area of the left thenar which was not yet desquamating, on February 8.

During the following days there was marked improvement in the condition of the palms. Three weeks after the incident the skin of the palms had healed and only slight erythema was left. The desquamation of the skin of the soles started much later. It reached its maximum

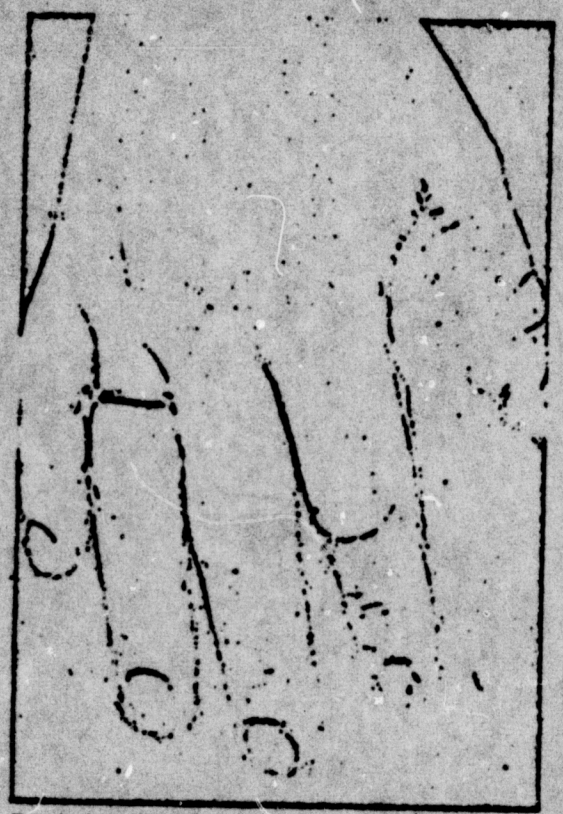

Fig. 1. Hand of the patient one week after the eating of the halibut liver.

Fig. 2. Foot of the patient, scaling at its maximum, three weeks after the incident.

after 3 weeks (Fig. 2), compared to one week for the hands. The slight desquamation of the rest of the body had entirely disappeared by then.

Laboratory findings

Hemoglobin 18.1 g%, erythrocytes 5.04 mill., W.B.C. 5300/mm³, bands 0, polymorphs 59, lymphocytes 32, monocytes 5, eosinophils 3, basophils 1. Blood sedimentation rate: 1/4. Total protein i.S.: 8.5 g%, alb.: 65.5%. Glob.: Alpha$_1$ 4%, Alpha$_2$ 7%, Beta 12%, Gamma 11.5%. Serum phosphorus 4.2 mg%, calcium 10.4 mg%, acid phosphatase 0.1 Bessey u., alkaline phosphatase 3.7 Bessey u., Thymol turbidity 1.8 u., urea 36 mg%, creatinine 0.7 mg%, SGOT 27 u., SGPT 23 u., total bilirubin 0.5 mg%.

Serum lipids (non-fasting): total lipoid 1283 mg%, phospholipoid 12.9 mg%, cholesterol 379 mg%, esters 73%.

These values show no remarkable deviation from the normal, except a slight increase in the L.D.H., 410 u. (norm. 360 u.), which had returned to normal on February 6 (280 u.). The total lipoid and cholesterol values are elevated even for a non-fasting state. In view of the well-known bleeding tendencies in cases of chronic hypervitaminosis A, coagulation studies were performed; all values were within normal limits: recalcification time 187", prothrombin time 15" (control 15"), fibrinogen content 510 mg%, antithrombine immediate: normal, bleeding time 1'42", thrombocytes 220,000 mm³, hematocrit 51%, color serum normal.

Serum vitamin A levels

The serum vitamin A level on February 7 (10 days after the incident) was 250 i.u./100 ml (norm. 80–120 i.u.), due to an intervening weekend this value was not determined until 2 1/2 days after the sample was taken. It is known (5) that serum vitamin A levels may decrease by 50% on standing for several hours. Technically it was not possible to reduce this interval to less than 24 hours. The second determination on February 13, gave a value of 355 i.u., carotene 50 microgram (normal). It is possible that the first value may have been too low as a result of the delay between the taking of the sample and the determination. On March 20, 51 days after the meal his serum vitamin A level was 310 i.u./100 ml.

Fig. 3. Histologic section of the left thenar showing hyperkeratosis, acanthosis and hyperemia of the dermis (× 100).

Histopathologic findings (Fig. 3)

The biopsy specimen showed a piece of skin with a very wide horny layer, in which slit formation was noticed. The epidermis was built regularly. There was a very wide stratum granulosum. The rete ridges were wide, the dermal papillae narrow. There was some edema and lymphocytic infiltration round the blood vessels of the dermis.

Conclusion: hyperkeratosis, acanthosis and hyperemia of the dermis. These changes are compatible with the diagnosis of vitamin A intoxication.

Follow-up data on the other crew members

The remaining crew members of the "Alida" were examined after their return from another journey to the Lofoten, on February 25, 28 days after the incident. The results are shown in Table I.

On February 25 all patients showed desquamation of hands and feet. None had suffered from dizzyness or blurred vision. Vitamin A levels were elevated in all. The highest level was found in case 1, which is the patient described in full in this paper. The trawler was in port again on March 20, 51 days after the incident, and the crew could be inspected once more. All symptoms had disappeared. An exception was patient number 4, who developed strong desquamation of the horny layer of the soles of the feet in the first week of March, which was still present on March 20. No changes remained elsewhere on the body. Vitamin A levels could be determined again in patients 1, 2, 3, 4, 8 and 9.

Table I

Serial no.	Age	Halibut liver (g)	I.U. vit. A/100 ml serum 25.2.69	20.3.69	Headache	Nausea	Vomiting	Desquamation face	Desquamation trunk	Desquamation hands	Desquamation feet	Ambulant	To bed	Part. ambulant, part. to bed
1	23	300	355	310	+++	+	−	+	+	+++	+++	−	+	−
2	30	250	250	225	++	+	−	+	−	−	−	−	−	+
3	54	150	225	225	++	−	−	+	−	−	−	+	−	−
4	32	50	255	350	++	−	−	+	−	++	+++	−	−	+
5	28	20	250		+	+	−	+	−	−	−	+	−	−
6	61	90	190		+	+	−	+	−	−	−	+	−	−
7	20	300	175		+++	++	++	+	+	+	+	−	+	−
8	25	200	155	135	++	+	+	+	+	+	+	−	+	−
9	31	50	120	155	+	−	−	−	−	−	−	+	−	−
10	46	150	195		++	++	++	+	+	+	+	−	+	−
11	47	20	180		+	−	−	−	−	−	−	+	−	−

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COMMENT

In the English translation of the diary of Gerrit de Veer (20), which describes the winter of 1596/1597 spent on the island of Nova Zemlya by a group of Dutch sailors led by Willem Barentsz and J. van Heemskerk, who were in search of the Northeast passage to India, the following passage is found on May 31, 1597. It concerns the shooting of a polar bear: "but her death did us more hurt than her life, for after we ript her belly, we drest her liver and eate it, which in the taste liked us well, but it made us all sicke, specially three that were exceeding sicke, and we verily thought that we should have lost them, for all their skins came of, from the foote to the head, but yet they recovered againe, for which we gave God heartis thankes". In the following centuries many whalers and arctic travelers became unpleasantly acquainted with the poisonous qualities of the livers of polar bear (3, 7, 8, 12, 19), and less frequently of eskimo husky (12, 18), bearded seal and greenland fox (18). Several cases of poisoning by fishliver have been recorded. Poslavski (15) described 9 patients who became ill after eating whale liver. Lonie (10) reported intoxication symptoms in a family after the ingestion of shark liver. Similar symptoms have been recorded after the eating of liver of "hapuka" (groper), kingfish, swordfish (8), ishinagi [stereolepis ishinagi (1)], Spanish mackerel (13), and red steenbras (16).

The symptoms of vitamin A intoxication were divided by Knudson (9), into those of acute and chronic intoxications, each occurring in children and adults. We shall limit ourselves to the acute intoxications in adults.

The following symptoms have been described regularly (3, 9, 10, 12, 15). Two to eight hours after the meal a very severe headache occurs, which is usually localized frontally, followed by nausea, vomiting, dizzyness, irritability tachycardia, a feeling of tiredness and an excessive urge to sleep (sometimes for 24 hours!). In the more severe cases there is redness of the face and sometimes of the mucous membranes. Usually there is localized or generalized pruritus. This is followed after 24–36 hours by peeling of the skin beginning around the mouth and spreading over the entire body. The skin of hands and feet sometimes comes off as a whole. Subconjunctival hemorrhages and gingivitis may occur. Usually the symptoms wear off in a few days, sometimes recovery takes longer. The desquamation lasts for several weeks. The symptoms in our patients are quite similar to those described in the literature of patients suffering from acute vitamin A intoxication after eating liver of polar bears, eskimo huskies, certain fish and after the ingestion of high dosages of vitamin A preparations (6). The patient reported in this paper had eaten halibut liver at other occasions without becoming ill. Fridtjof Nansen (14) reports eating polar bear liver in small amounts without ill effect. These observations may be explained by one of the following findings:

1. The concentration of vitamin A in halibut liver oil increases with the size of the liver and therefore with the size of the animal (11). In contrast to mammals, fish may continue to grow after reaching full maturity. As a result some fish in certain species may reach a very large size and weight. With increasing age the accumulation of vitamin A in the liver continues, since only small amounts of this vitamin are required.

2. There is a marked seasonal fluctuation in the vitamin A content of halibut liver oils. It may vary from 8000 i.u./g in February to 106,000 i.u./g in May (11). There is also a seasonal fluctuation in the amount of oil present in the liver. In general there seems to be an inverse relationship between the amount of oil in the liver and the vitamin concentration in the oil.

3. The part of the liver which is eaten may also play a role. The top of the liver lobe of the halibut contains the largest amount of vitamin A (2).

4. Finally the amount of liver eaten may have influence on the symptoms. It can be seen from Table I, that even small amounts of liver eaten have caused symptoms. If we take 100,000 i.u./g vitamin A as probable concentration (11) for this very large halibut liver, the ingestion of 20 g would be equivalent to a dose of 2 million units. Gerber considers this a sufficiently high dose to cause acute symptoms (4). Poslavski's patients developed symptoms exactly similar to those of our patients on dosages of 1–5 million units. It can be seen from Table I, that there is no relationship between the amount of liver eaten, the seriousness of the symptoms, and the serum vitamin A level, which is also in agreement with findings in the literature (6).

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Hepatic Injury in Chronic Hypervitaminosis A

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A 6-year-old girl who suffered from chronic hypervitaminosis A developed hepatosplenomegaly, hepatic dysfunction, and hypersplenism. A liver biopsy specimen displayed large lipid laden Kupffer's cells which were shown to contain vitamin A by fluorescence microscopy. Electron microscopically hepatic injury was indicated by increased lysosomes, focal cytoplasmic degradation, and numerous "light" and "dark" cells. These nonspecific indications of liver cell damage may reflect intracellular release of the biologically active alcohol of vitamin A.

The association of hepatosplenomegaly and chronic hypervitaminosis A has been recognized since the description of Josephs[1] in 1944. However, few clinicopathological correlations have been reported. In this communication we describe the hepatic changes observed by light, fluorescence, and electron microscopy in a 6-year-old girl with hepatic dysfunction and hepatosplenomegaly resulting from chronic excess ingestion of vitamin A.

Report of a Case

The patient was a 6-year-old white girl who was admitted with a diagnosis of "probable encephalopathy and intracranial hypertension." During the preceding ten days she had suffered from a febrile illness associated with a discharge from the right ear. The night before admission to North Shore Hospital she suddenly became limp and unresponsive. She was admitted to a local hospital where an intravenous infusion of glucose water was started. This was still running when she arrived at North Shore Hospital. The temperature, at that time, was 101 F (38.3 C); pulse rate, 72 beats per minute; respirations, 26 breaths per minute; blood pressure, 120/70 mm Hg; weight, 15.1 kg (33 lb); and circumference of the head, 50 cm. She was a pale, apathetic girl with dry skin, sparse scalp and eyebrow hair, marked cheilosis, and cracked and bleeding lips. The right eardrum was obscured by a sero-sanguinous discharge. A firm spleen was felt 3 cm below the left costal margin. The liver edge was 1 cm below the right costal margin. There was shotty generalized lymphadenopathy. Percussion of the head elicited a "cracked pot" sound. The sclerae were icteric and the optic nerve heads were blurred. The neck was supple. The hemoglobin level was 9.3 gm/100 ml; hematocrit reading, 29%; white blood cell count (WBC), 17,600/cu mm with

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70% neutrophils, 3% stab forms, and 29% lymphocytes. The urine had a specific gravity of 1.022, 3+ acetone, and 8 to 10 WBC per high power field. Sedimentation rate was 38 mm/hr. Total serum bilirubin level was 6.8 mg/100 ml (2.8 mg/100 ml indirect reacting). The other significant blood chemical findings were as follows: blood urea nitrogen (BUN), 10.6 mg/100 cc; carbon dioxide, 15 mEq/liter; sodium, 122 mEq/liter; potassium, 3.6 mEq/liter; and chloride, 122 mEq/liter.

Because of the hypokalemia and hyponatremia, she was given appropriate electrolyte containing fluids intravenously. Because of a reported penicillin sensitivity and the suspected ear infection, antibiotic treatment was started with erythromycin and oxytetracycline (Terramycin) and continued for four days. The morning after admission, she was much more alert. The blurring of the optic discs disappeared by the fourth hospital day. The serum bilirubin level slowly fell during the next few weeks. However, throughout her 4½ weeks in the hospital, the thymol turbidity remained between 6 and 10 units, and the activity of serum glutamic oxaloacetic transaminase (SGOT) stayed between 120 and 160 units. Approximately four weeks after admission, a percutaneous liver biopsy was performed.

The anemia noted on admission became more apparent as hydration improved, the hemoglobin level dropping to 6.5 gm/100 ml. The red blood cells (RBC) were normochromic. The platelet count was 24,000/cu mm. On the morning of the fourth day, she had a severe nose bleed which required cauterization. She then received the first of three transfusions—a total of 750 ml of whole blood was given. On the sixth day, the hemoglobin level was 10.5 gm/100 ml, and the hematocrit reading was 31%. The platelet count was 110,000/cu mm by the eighth day.

Shortly after admission additional significant history was obtained. Because the mother had been told that vitamins were good for the baby, the patient had received varying amounts of cod liver oil or vitamin drops with every feeding ever since she was 18 months old. A pint bottle of cod liver oil (approximately 400,000 units of vitamin A) or 1½ bottles of multivitamin drops (approximately 625,000 units of vitamin A) was consumed weekly. The diagnosis of hypervitaminosis A was confirmed nine days after admission when the blood level of free vitamin A was reported as 825μg/100 cc (normal 6 to 60μg). Radiographs of the long bones showed only moderate demineralization, metaphyseal irregularities, and widening of epiphyseal lines. No cortical hyperostoses were seen. There was no evidence of hypervitaminosis D.

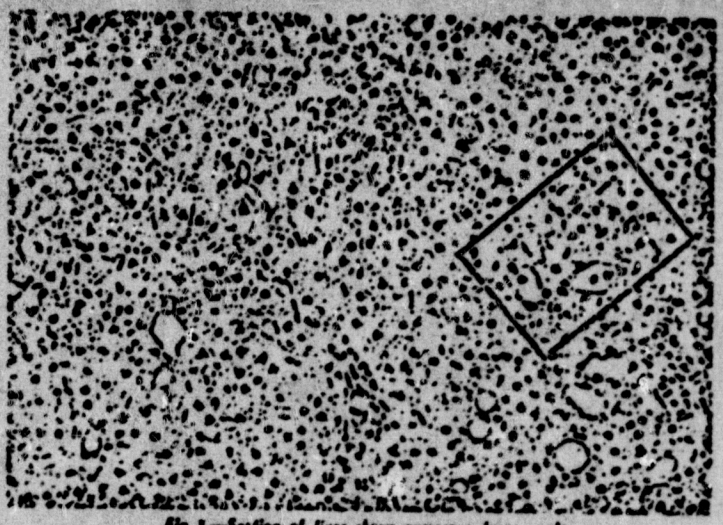

Fig 1.—Section of liver shows numerous large, pale vacuolated sinusoidal cells (hematoxylin and eosin, × 150).

Fig 2.—Higher power of previous figure (boxed area) showing enlarged vacuolated sinusoidal cells (hematoxylin and eosin, × 500).

When discharged one month after admission, she weighed only 15 kg (33 lb), but she was afebrile, alert, and active. Her appetite had improved. Although her hair was still sparse, the cheilosis and cracked lips were no longer prominent. However, a firm spleen was still felt 3 cm below the costal margin and the liver edge was still 1 cm below the costal margin.

One year later, she weighed 18.1 kg (40 lb), and had a good growth of scalp hair and eye lashes. The liver edge was no longer palpable, but the spleen was still firm and easily felt 3 cm below the costal margin. The hemoglobin

Fig 3.—Fluorescence micrograph of liver. Sinusoidal cells display intense cytoplasmic fluorescence. Hepatocytes (arrows) display faint fluorescence (× 450).

Fig 4.—Sinusoidal cell showing cytoplasm occupied by large lipid globule which displaces the nucleus (N) (× 14,400).

level was 8.9 gm/100 ml; hematocrit reading, 39%; RBC, 3,200,000/cu mm; reticulocyte count, 3.7%; platelet count, 313,000/cu mm; and WBC, 5,800/cu mm. Hypersplenism was thought to be the cause of the persistent anemia.

Morphologic Studies

The specimen of liver obtained by percutaneous aspiration with a Menghini needle was divided into three pieces. A portion of the specimen was fixed in 10% solution of neutral buffered formaldehyde solution, and from it paraffin sections were prepared for light microscopy. For electron microscopy, a small fragment was fixed in ice cold 1% osmic acid in veronal acetate, buffered at pH 7.4. After dehydration in graded alcohols, the tissue was embedded in epoxy resin (Epon 812) and thin sections cut on a microtome (Porter Blum). Sections were stained with lead hydroxide and examined with an electron microscope (Hitachi HS-7) in the Pathology Department at the Mount Sinai School of Medicine. The remaining portion of the specimen was snap frozen in 2-butyl alcohol at —70 C. Cryostat sections were examined under ultraviolet light with a fluorescence microscope. For comparison with spontaneous fluorescence, liver tissue from a patient with a nonhepatic disorder was examined in the same fashion.

Results

By light microscopy the lobular architecture was intact, with normal portal tracts and central canals (Fig 1). The liver cell plates were regularly arranged and the liver cells appeared normal, except for conspicuously increased lipofuscin pigment. Within the sinusoids there were numerous swollen littoral cells. Many of these had a foamy reticulated cytoplasm, while others had a clear cytoplasm (Fig 1 and 2). Several such cells were also seen in the portal tracts.

With fluorescence microscopy, the

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Fig 5.—Portions of four hepatocytes. Smooth endoplasmic reticulum (SER) is conspicuously hypertrophied. A sinusoidal mesenchymal cell contains a large fat globule (F). MN indicates mesenchymal cell nucleus; N, nucleus (× 5,500).

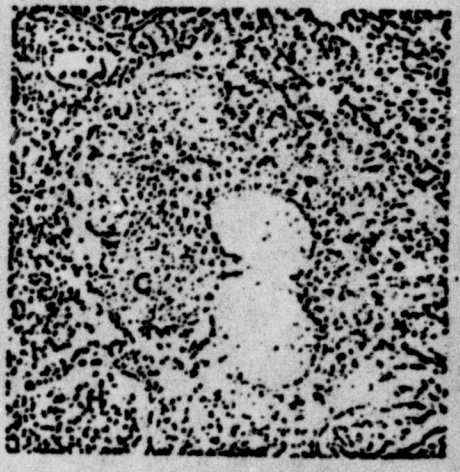
control specimen showed faint fluorescence in Kupffer's cells and occasional fluorescent granules in hepatocytes. In the biopsy from the patient numerous littoral cells and occasional mesenchymal cells in the portal tracts displayed intense green cytoplasmic fluorescence (Fig 3), which faded rapidly with continued exposure to ultraviolet light. Slight diffuse fluorescence was noted in occasional hepatocytes. Fluorescent granules in hepatocytes were common.

Electron microscopic examination revealed numerous sinusoidal cells containing large fat droplets, which occupied most of the cytoplasm (Fig 4 and 5). Similar cells were seen in the portal tracts. In some portal tracts lipid globules which appeared extracellular were noted (Fig 6).

In the hepatocytes the endoplasmic reticulum, mitochondria, and bile canaliculi appeared normal. With respect to other subcellular organelles, the hepatocytes presented a varied appearance, some being entirely normal, while others displayed one or more of the following abnormalities.

(1) Pigment. Most hepatocytes exhibited a variable number of irregularly shaped, heterogeneous, electron opaque bodies composed of sub-

Fig 6.—Portal tract contains extracellular lipid. C indicates collagen; H, hepatocyte (× 10,500).



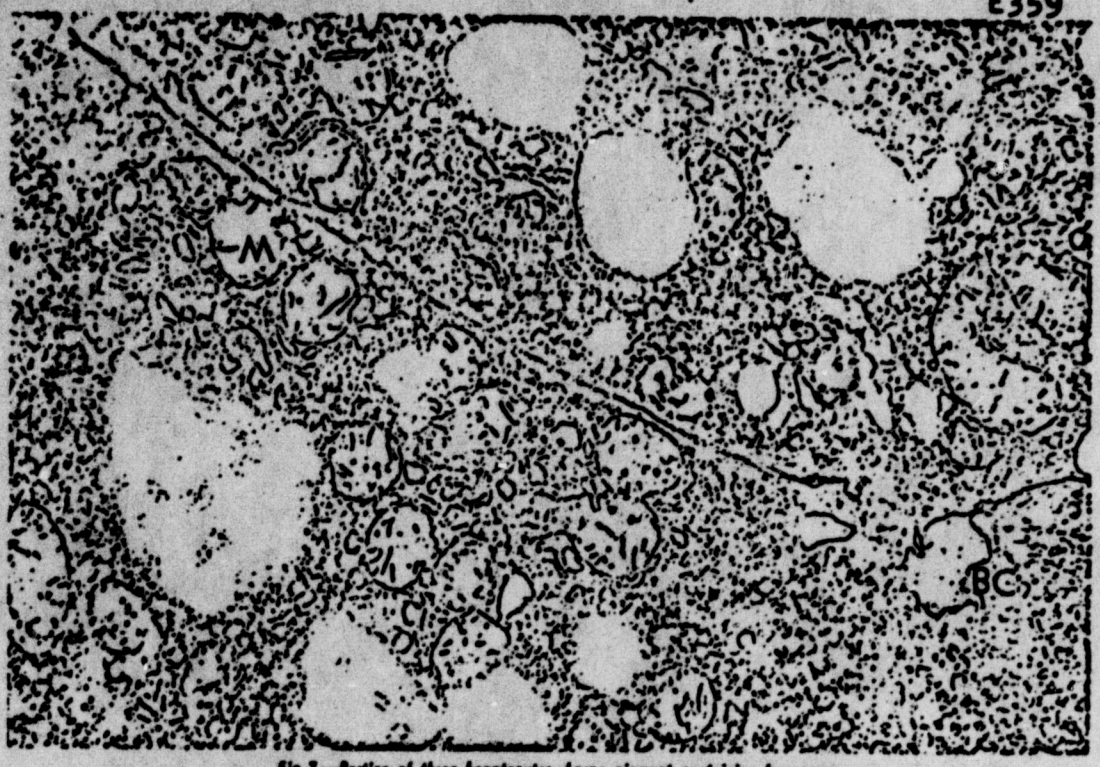


Fig 7.—Portion of three hepatocytes. Large pigment containing lysosomes are conspicuous. BC indicates bile canaliculus; M, Mitochondrion (X 14,400).

structures of a variable density (Fig 7 and 8). These were interpreted as lysosomes, were particularly prominent near bile canaliculi, and corresponded to the lipofuscin pigment granules seen by light microscopy.

(2) Focal cytoplasmic degradation was conspicuous, being characterized by numerous small vacuolated foci, which were not delimited by a membrane. Within these residual vacuolated bodies were irregular osmiophilic bodies in the forms of clumps, whorls, and irregular figures, which appeared to be degenerated organelles (Fig 9). Autophagic vacuoles, limited by a single membrane and containing degenerated organelles, were also increased (Fig 8).

(3) Fat. Many hepatocytes contained small lipid droplets (Fig 8).

(4) Smooth endoplasmic reticulum was hypertrophied in a moderate number of hepatocytes (Fig 5).

In addition to these changes, an increased variability in the density of hepatocytes—so-called light and dark cells—was present (Fig 8).

Hematologic Studies

A variety of tests was carried out to find the cause for the normochromic and normocytic anemia. The bone marrow was highly cellular and contained abundant megakaryocytes, but was otherwise unremarkable. The Coombs' test was negative. Starch block hemoglobin electrophoresis demonstrated 1.8% A^2 hemoglobin and 1.5% fetal hemoglobin. The glucose-6-phosphate dehydrogenase activity of the erythrocytes was normal. Three weeks after the last transfusion the patient was injected with her own erythrocytes labeled with radioactive chromium (^{51}Cr). The half-life of erythrocytes labeled with ^{51}Cr was 17 days (normal 27 to 35 days) and splenic sequestration was demonstrated.

Comment

The clinical appearance of the patient was similar in most aspects to that described in chronic hypervitaminosis A.[2-4] The mild jaundice, hepatosplenomegaly, and course resembled that of the child described by Josephs.[1] The diagnosis in our patient was established not only by the high blood level of vitamin A, but also by the demonstration of increased vitamin A-like fluorescence in the liver biopsy specimen.[5] In a review of 36 cases of hypervitaminosis A, Oliver [2] pointed out that the signs and symptoms are highly variable, and that individuals and organ

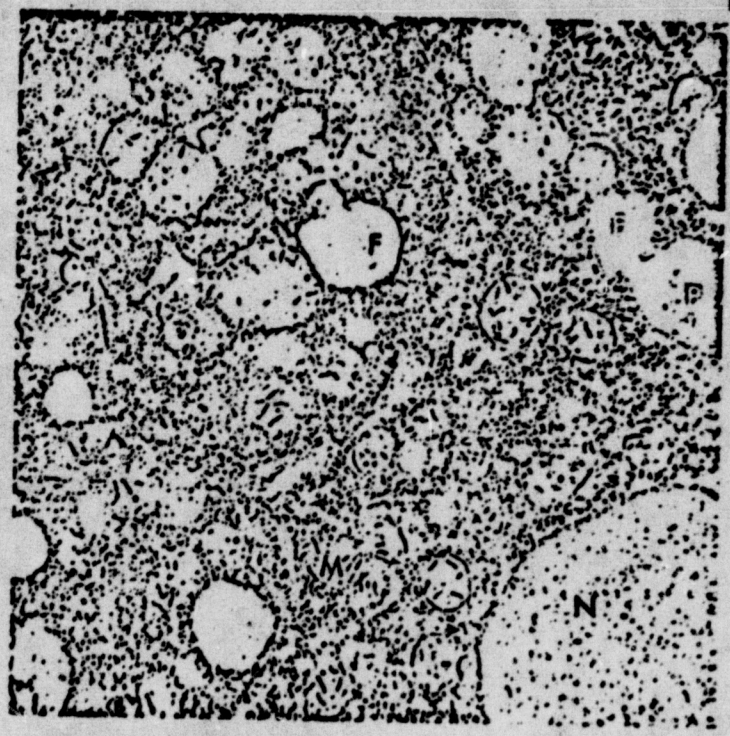


Fig 8.—Two neighboring hepatocytes, a dead cell on the left and a light one on the right. Both contain fat droplets (F). An autophagic vacuole (arrow) contains a degenerated mitochondrion. P indicates pigment; N, nucleus; M, mitochondrion; G, glycogen (× 10,600).

systems may vary in their susceptibility to the toxic effects of vitamin A. This may be why the liver and spleen were so prominently involved in our patient.

Hepatosplenomegaly was described in Josephs'[1] original case report and has been observed in subsequent cases of hypervitaminosis A. Nevertheless, we find only two previous reports of liver biopsies.[6,7] Both were in adults, and by light microscopy, were reported as normal, except for lipid droplets in Kupffer's cells in one case.[7] In that case, minimal hepatic dysfunction, characterized by slight prolongation of the prothrombin time and mild elevation of serum alkaline phosphatase activity was noted.

Jaundice, elevated thymol turbidity, and increased activity of SGOT in our patient were clinical evidence of hepatic dysfunction. By light microscopy, the hepatic sinusoids contained large foamy macrophages which displayed the characteristic evanescent fluorescence of vitamin A. Similar fluorescence was also seen within hepatocytes. Hepatic lipofuscin pigment, which is uncommon in children, was prominent in this patient. Electron microscopically, the fluorescent material seen with ultraviolet light corresponded to the large fat droplets in Kupffer's cells, small droplets in hepatocytes, and fat in the portal tracts. Ultrastructural changes in hepatocytes included increased pigment containing lysosomes, lipid droplets, focal cytoplasmic degradation, and increased variability in electron density of

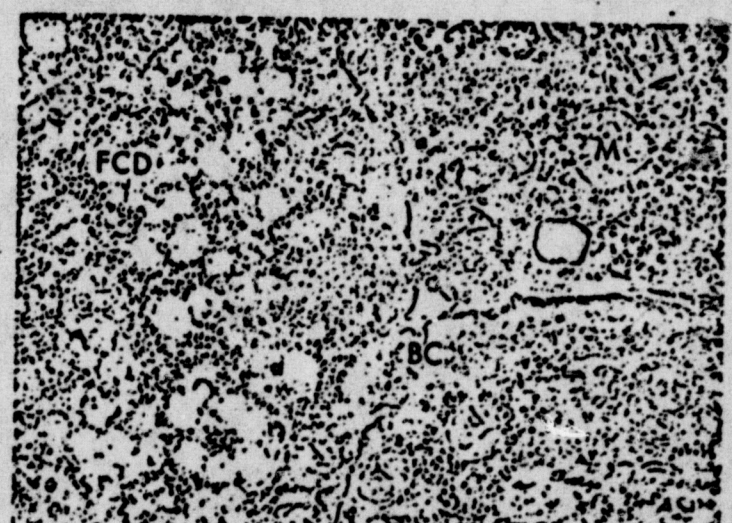


Fig 9.—Portions of four hepatocytes. Striking focal cytoplasmic degradation (FCD) is noted. G indicates glycogen; BC, bile canalicolus; M, mitochondrion (× 10,600).

neighboring cells (so-called light and dark cells). These changes probably indicate cell damage, but are nonspecific and may be observed in diverse conditions such as viral hepatitis [8] or alcoholic liver injury.[9] Thus, the hepatic storage of vitamin A in this case was associated with both clinical and structural evidence of liver damage. The hypertrophy of smooth endoplasmic reticulum, which has also been previously noted,[7] is probably a response to increased metabolism of vitamin A, since both synthesis [10] and splitting [11] of the ester are microsomal functions.

The anemia associated with chronic hypervitaminosis A is usually attributed to poor nutrition or blood loss. Although these factors may have played a role in our patient, she still had mild anemia and reticulocytosis one year after stopping the ingestion of excess vitamin A. By that time her appetite had improved and she had gained weight. However, her spleen was still very large. The hypersplenism, demonstrated during her hospital admission by studies with erythrocytes labeled with ^{51}Cr, probably accounted for her continuing anemia, even though her platelet and leukocyte counts had returned to normal levels.

Vitamin A is transported from the intestine to the liver in the esterified form and stored there as the biologically inactive ester.[12] Hepatic esterases convert it to the biologically active alcohol, which is released into the blood. Excess free vitamin A results in rapid hemolysis of erythrocytes in vitro,[13] alters the appearance and function of embryonic chick cartilage,[14] and induces changes in isolated rat liver mitochondria [15] and lysosomes.[16] The mitochondria swell and the lysosomes release hydrolytic enzymes. These phenomena have been explained by the theory that excess free vitamin A penetrates cellular and intracellular membranes and changes their function.[16] Toxic blood levels of vitamin A in man result not only from excessive intake, but also from an interference with the ability of the liver to control the hydrolysis and release of vitamin A.[12] If excessive amounts of biologically active vitamin were released within a hepatocyte, changes might occur in the lipoprotein membranes of the intracellular organelles. The increase in lysosomes and the focal cytoplasmic degradation seen in our biopsy specimen would be compatible with such an effect.

This investigation was supported in part by Public Health Service grants AM-03846, AM-10833, and AM-07538.

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Your editorial thus oversimplifies complex phenomena. It implies that all post cardiotomy psychiatric problems are, in effect, merely the product of brain damage produced during the operation. My concern is that the role of a variety of other factors may thus be overlooked and patient care seriously compromised. Earlier reports indicated that patients often experienced a lucid interval of three to four days following surgery and preceding the onset of disorganized mentation.[2-4] This disorder usually cleared within 24 to 48 hours after transfer to a standard hospital environment. These clinical observations suggested that postoperative factors, and specifically the Open-Heart Recovery Room environment, might be playing a role in the production of those symptoms. Subsequently Lazarus and Hagens were able to significantly reduce the incidence of these postoperative psychiatric complications by manipulating a variety of environmental and psychological variables. We agree with Tufo that it is the patient with an organically impaired brain who is most vulnerable to the sleep deprivation and sensory monotony often presented in this environment.

We have observed another smaller group of patients in whom confusion, disorientation, or delirium were apparent on the first postoperative day (D. S. Kornfeld et al, unpublished data).[5,6] These patients were clearly manifesting the effects of organic brain dysfunction produced during surgery. Obviously, in these patients, the postoperative environment could not have contributed to their disorder. It may be that the Tufo series, with its predominantly early onset of symptoms, contains a larger proportion of patients in this latter category.

DONALD S. KORNFELD, MD
New York

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To the Editor.—Your editorial "Open-Heart Surgery and the Psyche" (212:1370, 1970) is so dogmatic and final! Need there be a "victor?" I think the comments are oversimplistic and show a naivety of the mind-body problem which is frankly rather frightening. If you really read my work, as well as that of others (such as Kornfeld et al),[1] you will find no assertion that all the psychiatric complications following open-heart operations are "functional" in nature. For we are all aware there are a *multiplicity* of factors involved in the patient's response to cardiac operations. Indeed I mention Gilman's article[2] in my original paper,[3] and in other writings note "multiple etiologies" involved in postoperative reactions. At a time when psychiatry is moving toward medicine and psychiatrists are collaborating with their medical and surgical colleagues to understand the *complexity* involved in patients' responses to physical illnesses and operative procedures, let us not attempt to start battles where they do not exist.

HARRY H. ABRAM, MD
Charlottesville, Va

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Need for Controlled Study

To the Editor.—The article by Sheldon et al on venous autografts for myocardial revascularization (213:18, 1970) records a magnificent surgical series from the standpoint of concept and technical ability. Yet the very appealing evidence for success remains inconclusive. Where are the control patients? Surgery is a form of therapy, not a magical process. It must be evaluated like other treatments and by equally high standards, ie, by minimizing bias through random allocation of "qualifying" patients to control and treated groups.

It is equally deplorable that in the same issue (QUESTIONS AND ANSWERS, p 135) Dr. Baue's evaluation of various forms of revascularization is devoid of any reference to the lack of control. My criticism of the surgical enthusiasts is not that they are wrong (or even probably wrong), but rather that they have not attempted to really prove themselves right. Their technical and professional expertise are not in question. The absence of properly designed and controlled studies cuts both ways—the proof remains in limbo.

Again in the same issue (p 131), John Oates rightly deplores the absence of a control series in the report on exercise therapy for hypertension. The points in the reply are well made, but are only tangentially relevant to the real issue.

We would not think of testing a new drug without control patients. Surgical procedures generally are perilous far beyond the side effects of most pills. It is high time that granting authorities, journal reviewers, and therapeutic trials committees demand equal standards of all treatments: appropriately designed and controlled trials.

DAVID H. SPENCER, MD
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Papilledema and Hypervitaminosis A

To the Editor.—The letter by Podontin (212:628, 1970) describing the case of pseudotumor cerebri produced in an 18-year-old girl by hypervitaminosis A, includes the statement, "In none of the cases—adults or children—has papilledema been the only finding." This patient was observed at Ohio State University Hospital.

Oliver and Havener[1] described in 1958 the case of a 14-year-old girl with bilateral papilledema, as well as loss of hair, skin changes, migratory arthritic pains, hepatomegaly and splenomegaly, hypomenorrhea, and generalized malaise. Serum vitamin A levels confirmed the diagnosis of hypervitaminosis A.

Morrice et al[2] in 1960 described three cases in girls 14, 15, and 16 years with diplopia, papilledema, and other symptoms suggesting brain tumor. In addition to various individual complaints, each had hypomenorrhea, alopecia, and rhagades or other marked forms of dermatosis.

Ironically, these four additional cases of papilledema due to hypervitaminosis A were all observed at University and Children's Hospitals associated with Ohio State University.

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(Continued from page 531)

pregnancies associated with an I.U.D. A case of ovarian pregnancy associated with an I.U.D. was reported by Piver, Baer and Zachary.[4] This subject has recently been explored by Lehfeldt, Tietze and Gorstein.[5]

Does the presence of an I.U.D. increase the incidence of ectopic pregnancy? Wei,[6] quoting other authors and also from his own experience, believes that it does not, but the question is by no means decided.

I wish to thank Dr. Meredith Silver for examining the surgical specimen.

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Christmas tree allergy

To the Editor:

In their paper "Christmas tree allergy: mould and pollen studies" (*Canad Med Ass J* 103: 1272, 1970) Wyse and Malloch describe 34 patients with skin symptoms and signs which they attribute to Christmas tree allergy. In Table IV they list the following:

Skin:	Transitory rash.....	28 patients
	Vesicles and exudate	1
	Angioedema	3
	Urticaria.....	2

The authors describe the transitory rash as "multiple small, red, itchy or burning spots on the forearms and hands and occasionally on the face, where the skin had contacted the needles; this started within five minutes of trimming or decorating the tree and usually disappeared within half an hour." They suggest that this rash "probably represents a contact allergy to the oleoresin of the balsam".

The morphologic term "spot" does not indicate whether these are macules, papules, patches, plaques, or variants thereof, but the rapid onset of the skin rash does not agree with a diagnosis of contact allergy.

Contact allergic dermatitis is mediated by delayed cellular immune mechanism and does not arise and disappear within minutes. The "transitory rash" which the authors describe is presumably a primary irritant dermatitis due to the contact with the Christmas tree needles or other products of the tree such as bark or resin. Any individual is subject to a similar primary irritant reaction and it does not require stimulation of the allergic process.

Details are not given of the single patient with "vesicles and exudate", but this is a morphologic presentation that may often be seen with contact allergic dermatitis (e.g. as in poison ivy).

True contact allergic dermatitis to numerous products of trees (resins, pollens, sawdust etc.) is well known and well documented in standard texts.[1,2]

Scratch tests are not accurate in contact allergic dermatitis and should not supplant the regular patch test.

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Vitamin A intoxication

To the Editor:

I should like to bring to the attention of the profession the risks of vitamin A intoxication and the ease with which this vitamin can be obtained by over-the-counter sales in this country.

I recently attended a girl aged 15 who developed headaches, vomiting and diplopia, all with acute onset. Strabismus and papilledema were evident on examination and the cerebrospinal fluid pressure was grossly elevated. My original diagnosis was a probable cerebral tumour but extensive neurological investigation was completely negative. The patient had been taking vitamin A in a dosage of 200,000 units daily for two years. She made a complete and dramatic recovery following discontinuation of this medication.

The vitamin had been sold to her over the counter in the drug store in the belief that it would benefit her facial acne. The strength of each tablet was 50,000 units, and while it was recommended on the bottle that only one tablet should be taken each day, the patient was told that it was quite common to take more than this in the treatment of acne. It seems to me that there is a very high risk of inducing "benign intracranial hypertension" in some patients if this vitamin is to be freely available without prescription.

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[Editor's note: A statement by the Canadian Paediatric Society on "The Use and Abuse of Vitamin A" appears on page 521 of this issue.]

(Continued on page 535)

Recent reports have brought hospitals for the mentally handicapped under timely scrutiny, but have prompted the point of view that the hospital is an inherently bad institution for the care of the mentally handicapped. This is unfair, because with the exception of a few newly established units most hospitals for the mentally handicapped in this country have not enjoyed the facilities, resources, and staff required to do justice to their patients.

Manswood Park Hospital, Lords G. D. A. SPENCER.

HYPERVITAMINOSIS A WITH HYPERCALCÆMIA

SIR,—A relationship between vitamin-A intoxication and hypercalcæmia is not generally recognised.[1] Large-dosage vitamin-A capsules may be readily purchased without prescription. We have seen a patient with severe hypercalcæmia associated with hypervitaminosis A. He was taking the vitamin because he had heard that it was beneficial in acne.

A 16-year-old male was transferred from another hospital because of hypercalcæmia of 18·9 mg. per 100 ml., detected by routine admission screening. He admitted to having taken vitamin A for about 6 months, usually 100,000 units a day, but every 4th or 5th day 300,000 units, for treatment of acne. In addition, he was taking vitamin C 500 mg. a day and a multiple-vitamin preparation containing vitamin A 5000 units, vitamin D 400 units, vitamin B_1 2 mg., vitamin B_2 2·5 mg., niacinamide 20 mg., vitamin C 50 mg., vitamin B_6 1 mg., vitamin B_{12} 1 µg., and calcium pantothenate 1 mg. He was also intermittently using an ointment containing vitamins A and D. Several weeks before admission he had developed polyuria and polydipsia, and about five days before admission a sore throat and swollen tender cervical lymph-nodes. The next day he had been feverish (102 °F) and had vomited several times. Two days later he had had general malaise associated with desquamation of the skin about his trunk, upper extremities, and face, along with facial flushing and fissuring of the lips.

On physical examination the patient was dehydrated, confused, and lethargic. The above cutaneous findings were noted. The liver was not palpable. Serum calcium was 18·9 mg. per 100 ml., CO_2 32 mM/l per litre, chloride 98 meq. per litre, potassium 3·2 meq. per litre, alkaline phosphatase 26 units, blood-urea-nitrogen (B.U.N.) 28 mg. per 100 ml., serum-glutamic-oxaloacetic-transaminase (S.G.O.T.) 91 units, and serum-proteins 6·9 g. per 100 ml. (3·2 g. albumin and 3·7 g. globulin). (These determinations were all performed on the 'Auto-Analyzer'.) Repeat calcium determinations before treatment were 18·4 mg. per 100 ml. and 16·7 mg. per 100 ml. The urinary excretion of calcium initially was 1045 mg. per 24 hours. Complete blood-count, serum-protein electrophoresis, and chest X-ray were normal. Urinalysis revealed a trace of protein and 10–15 white blood-cells.

He was started on a sodium-sulphate infusion with added potassium, and surgical exploration was undertaken on the evening of transfer because of the possibility of hyperparathyroid crisis. Four parathyroid glands were found, and all felt normal. One was removed, another biopsied, and a lymph-node was removed. All were histologically normal. He was continued on sodium sulphate and cortisone acetate, 100 mg. every 8 hours, after surgery. On the third hospital day the serum-calcium was 12·5 mg. per 100 ml. and on the fifth day it was 9·7 mg. per 100 ml.; it remained in the normal range when treatment was stopped. The serum-alkaline-phosphatase, urinary calcium, B.U.N., and S.G.O.T. were normal by the eighth hospital day. A prolonged prothrombin-time (35%) was corrected with parenteral vitamin K. Bromsulphthalein excretion was normal. An intravenous pyelogram, bone survey, and bone-marrow examination were normal. The vitamin-A preparation was examined for vitamin-D contamination by gas-liquid chromatography, thin-layer chromatography, and by spectrophotometry. By these sensitive techniques no evidence of contamination was found. The vitamin-A level was 934 I.U. per 100 ml. (normal 65–275 I.U. per 100 ml.), and the serum-carotene level was normal.

An association between experimental and clinical vitamin-A intoxication and increased bone resorption has been reported previously.[2,3] Vitamin-A intoxication associated with hypercalciuria has been described,[4] but only one case has been reported with hypercalcæmia (13·5 mg. per 100 ml.).[5] Our patient had dermatological and hepatic[6] findings of hypervitaminosis A in association with a high circulating level of vitamin A. Thus, the only apparent explanation for the hypercalcæmia was vitamin-A intoxication. We suggest that this should be considered in the differential diagnosis of hypercalcæmia.

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ACUTE HYPERCALCÆMIC SYNDROME DURING TREATMENT OF OSTEOPOROSIS WITH CALCIUM INFUSION

SIR,—Pak et al.[7,8] put forward the hypothesis that osteoporosis is caused by an imbalance between parathyroid-hormone secretion and calcitonin secretion, resulting in a net loss of bone. To reverse this imbalance they induced intermittent hypercalcæmia in 6 osteoporotic patients by means of 12 infusions of calcium (15 mg. per kg. body-weight per infusion) in 12–21 days. Each infusion lasted 4 hours. Their results were very promising and stimulated interest in this form of treatment.[9]

We have given calcium infusions to 7 patients with osteoporosis (results to be published later). 1 patient, a 70-year-old woman, developed a severe hypercalcæmic syndrome during the 5th infusion. Plasma-calcium was 20·2 mg. per 100 ml. She was treated with phosphate and glucocorticoids intravenously, but her condition improved only after 4–5 days. Before treatment plasma-creatinine was 12 mg. per 100 ml., but ^{51}Cr-E.D.T.A. clearance showed a glomerular filtration-rate of 36 ml. per 1·75 sq. m. body surface per minute. During the first calcium infusion, plasma-calcium increased from 10·2 mg. per 100 ml. to a maximum of 16·4 mg. per 100 ml., and 20 hours after the infusion it was 13·8 mg. per 100 ml.

On the basis of this experience we suggest that calcium infusions should only be used in treating osteoporosis if (1) the glomerular filtration-rate is normal, and (2) plasma-calcium has returned to normal after the previous infusion.

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AMERICAN ACADEMY OF PEDIATRICS
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THE USE AND ABUSE OF VITAMIN A

VITAMIN A is an essential nutrient necessary for maintenance of normal epithelial tissue and for optimal growth.[1,2] Impaired dark-adaptation and night blindness are well known manifestations of vitamin A deficiency. Although vitamin A is present in many foods, it cannot be assumed that all individuals receive adequate amounts. Preliminary reports from the recent 10-state nutrition survey* show that a significant proportion of the population has a low intake of vitamin A and low plasma vitamin A levels. Thus it would appear important to improve the diet of a considerable segment of the population or provide a vitamin A supplement for them.

Vitamin A is found in food in carotenoids, which are converted to vitamin A in the intestine; or, it may be preformed, as in foods from animal sources (or in diet supplements). There is no danger of excessive intake of vitamin A when carotenoids are ingested.

The recommended daily allowances of vitamin A are: for infants and children up to age 12 years, from 1,500 to 4,500 I.U.; for adults, 5,000 I.U.; and for pregnant women 6,000 I.U.[3,4] Although diets of many individuals provide higher levels of vitamin A, there are no known advantages in exceeding these allowances in normal individuals.

Thus, for prophylactic use or as a safeguard against inadequate intake, there are properly formulated supplements available on the market, i.e., those that contain 1,500 to 4,000 I.U. for infants and children, 5,000 I.U. for adults, and 6,000 I.U. for pregnant women.

However, excessive intake of preformed vitamin A may result in serious and potentially toxic effects. The easy availability of vitamin A in large doses without prescription exposes individuals to the danger of severe clinical toxicity. Physicians should be aware of the circumstances in which vitamin A toxicity may occur and its clinical manifestation.

Doses of 25,000 I.U. or more of vitamin A, which are present in some vitamin preparations, should not be used, unless severe deficiency of vitamin A, documented by an abnormally low blood level, exists. These doses taken daily for an extended period of time pose a risk, particularly to the pregnant woman and fetus. Studies in pregnant animals have shown that large doses of vitamin A produce central nervous system anomalies with hydrocephalus, encephalocoele, and other teratological effects in the offspring.[5,6] Infants may develop a bulging fontanel or hydrocephalus when given about 10 times the recommended daily allowance of vitamin A for several weeks.[7-9] The older child or adult with hypervitaminosis A manifests pseudotumor cerebri, a syndrome that may simulate the presence of an intracranial neoplasm, with signs and symptoms of unlocalized increased intracranial pressure,[10-12] such as headache, nausea, vomiting, lethargy, tinnitus, and diplopia. Physical findings are usually limited to the eyes, with sixth nerve paresis, papilledema, and, in long-standing cases optic atrophy and even blindness. Ingestion of as little as 25,000 to 50,000 I.U. of vitamin A per day for as short a period as 30 days can induce signs of increased intracranial pressure. Nonspecific findings encountered at all ages include dry skin and mucous membranes, sparse hair, brittle nails, myalgia, bone pain, arthralgia, abdominal pain, splenomegaly and hypoplastic anemia with leukopenia.

Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through

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easy availability of high potency vitamin preparations without prescription and by the overzealous parent who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods.

Serious problems of hypervitaminosis A have arisen in the use of large doses of vitamin A in treatment of acne vulgaris in adolescents. The clinical impression that high doses of vitamin A (50,000 I.U. to 150,000 I.U. per day) over a prolonged period are beneficial treatment for acne vulgaris has not been validated by well controlled clinical trials, nor is the rationale for this method of treatment clear.[19]

Vitamin supplements with proper levels of vitamin A for infants, children, adults, and pregnant women are available on the market. These should be prescribed when indicated. Vitamin supplements containing more than the daily doses recommended (8,000 I.U.) should not be used.

CONCLUSION

The grave risks resulting from the unrestricted sale of high concentrations of vitamin A make it imperative that an active curb, by appropriate legislation if necessary, be placed on the over-the-counter marketing of *high potency* vitamin A preparations. Physicians should be aware of the vitamin A content in the preparations they prescribe for their patients. They also should caution parents regarding the dangers of overdosage of this vitamin.

Committee on Drugs
SUMNER J. YAFFE, M.D., *Chairman*
Committee on Nutrition
L. J. FILER, JR., M.D., *Chairman*

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COMMITTEE A

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